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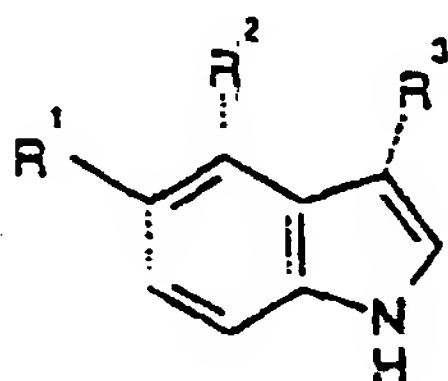
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9226537.0 21 December 1992 (21.12.92) GB(71) Applicant (for all designated States except US): SMITHKLINE
BEECHAM PLC [GB/GB]; New Horizons Court, Brentford,
Middlesex 9EP TW8 (GB).

(72) Inventors; and

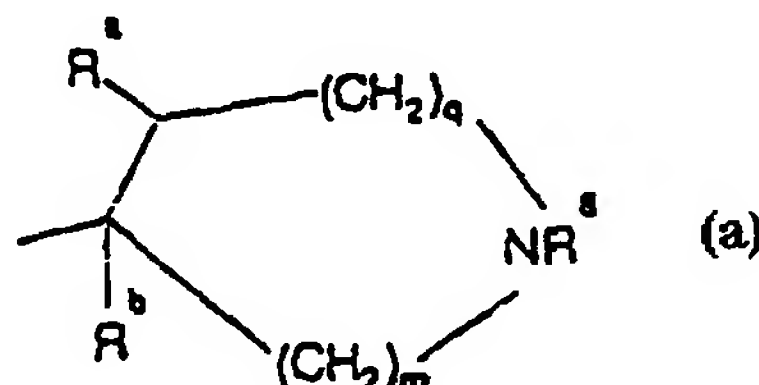
(75) Inventors/Applicants (for US only): PORTER, Roderick, Alan
[GB/GB]; SmithKline Beecham Pharmaceuticals, The Fry-
the, Welwyn, Hertfordshire AL6 9AR (GB). COATES,
William, John [GB/GB]; SmithKline Beecham Pharmaceu-
ticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB).(74) Agent: THOMPSON, Clive, B.; Corporate Intellectual Prop-
erty, SmithKline Beecham, Mundells, Welwyn Garden City,
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(54) Title: TRYPTAMINE ANALOGUES AS 5-HT₁-LIKE AGONISTS

(I)



(a)

(57) Abstract

A compound of structure (I), in which R¹ is an optionally substituted 6- to 10-membered aryl or heteroaryl ring; suitably R¹ is an optionally substituted 6- or 10-membered aryl ring such as phenyl or naphthyl; suitably R¹ is an optionally substituted 6- to 10-membered heteroaryl ring containing from 1 to 4 nitrogen atoms. R² is hydrogen, halogen, C₁₋₄ alkyl, CN, NO₂ or CF₃; R³ is hydrogen, halogen, C₁₋₄ alkyl, CN, NO₂ or CF₃; R³ is C(R⁴)(R⁵)CH₂NR⁶R⁷, -CH=NNHC(NH)NH₂ or a; R⁴ and R⁵ are independently hydrogen or C₁₋₄ alkyl; R⁶ and R⁷ are the same or different and are each hydrogen or C₁₋₄ alkyl or together with the nitrogen atom to which they are attached form a ring; R⁸ is hydrogen, C₁₋₄ alkyl, or C₃₋₆ alkenyl; R^a is hydrogen and R^b is hydrogen or hydroxy, or R^a and R^b together represent a bond; and q and m are independently 1 or 2; and pharmaceutically acceptable salts, solvates and hydrates thereof. The compounds are 5-HT₁-like agonists (or partial agonists) and as such are expected to have utility in medicine in the treatment and/or prophylaxis of migraine, and other conditions associated with cephalic pain, such as cluster headache, headache associated with vascular disorders and other neuralgia. They are also expected to have utility in the treatment or prophylaxis of portal hypertension.

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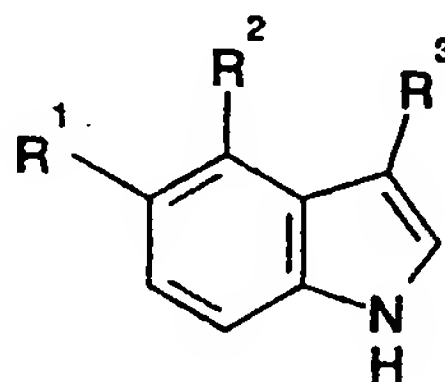
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TRYPTAMINE ANALOGUES AS 5-HT₁-LIKE AGONISTS

The present invention relates to novel tryptamine analogues, processes and intermediates useful in their preparation, pharmaceutical compositions containing them and their use in therapy, in particular for the treatment and/or prophylaxis of disorders characterised by excessive vasodilatation, such as migraine and portal hypertension.

The present invention therefore provides, in a first aspect, a compound of structure (I):



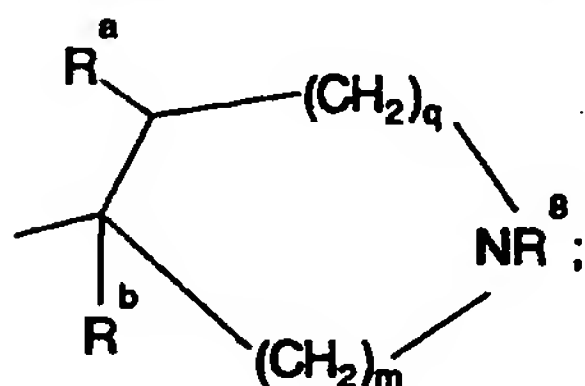
Structure (I)

in which

R¹ is an optionally substituted 6- to 10-membered aryl or heteroaryl ring;

R² is hydrogen, halogen, C₁₋₄alkyl, CN, NO₂ or CF₃;

R³ is C(R⁴)(R⁵)CH₂NR⁶R⁷, -CH=NNHC(NH)NH₂ or



R⁴ and R⁵ are independently hydrogen or C₁₋₄alkyl;

R⁶ and R⁷ are the same or different and are each hydrogen or C₁₋₄alkyl or together with the nitrogen atom to which they are attached form a ring;

R⁸ is hydrogen, C₁₋₄alkyl, or C₃₋₆alkenyl;

R^a is hydrogen and R^b is hydrogen or hydroxy, or R^a and R^b together represent a bond; and

q and m are independently 1 or 2;

and pharmaceutically acceptable salts, solvates and hydrates thereof.

Suitably R¹ is an optionally substituted 6- or 10-membered aryl ring such as phenyl or naphthyl.

Suitably R¹ is an optionally substituted 6- to 10-membered heteroaryl ring containing from 1 to 4 nitrogen atoms. Examples of such heteroaryl rings include pyridine, pyridazine, pyrimidine, pyrazine, triazine, quinoline, or quinazoline. Particular examples are pyridine, pyridazine, pyrimidine, pyrazine or quinoline.

The heteroaryl ring can be linked *via* a carbon or nitrogen atom of the heteroaryl ring.

Suitably R^1 is unsubstituted or substituted by up to 3 groups selected from halo, C_{1-4} alkyl, hydroxy, oxo, C_{1-4} alkoxy, $-CO_2R^9$, $-NHCOR^9$, $-CONR^{10}R^{11}$,
 5 $-SO_2NR^{10}R^{11}$, $-NHCO_2R^{12}$, NO_2 , $-NR^{10}R^{11}$, $NHCONH_2$, CN, CF_3 or CF_3O wherein R^9 to R^{11} are independently hydrogen or C_{1-4} alkyl and R^{12} is C_{1-4} alkyl.

Suitably, R^2 is hydrogen, halogen, C_{1-4} alkyl, CN, NO_2 or CF_3 . Preferably R^2 is hydrogen or halogen, in particular hydrogen or chlorine.

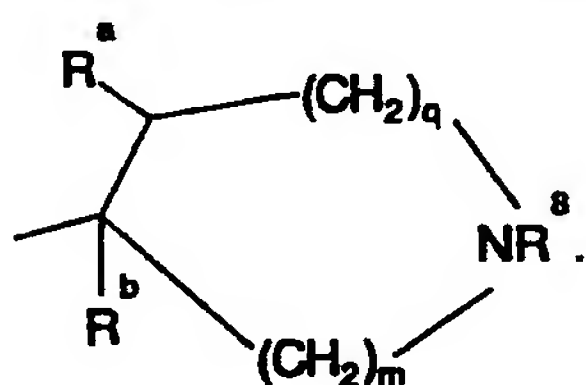
Suitably R^3 is $C(R^4)(R^5)CH_2NR^6R^7$ or $-CH=NNHC(NH)NH_2$.

10 Suitably, R^4 and R^5 are hydrogen or C_{1-4} alkyl. Preferably R^4 and R^5 are both hydrogen or methyl.

Suitably, R^6 and R^7 are the same or different and are each hydrogen or C_{1-4} alkyl or together with the nitrogen atom to which they are attached form a ring. Preferably R^6 and R^7 are both hydrogen or methyl.

15 Suitable rings formed by R^6 and R^7 together with the nitrogen atom to which they are attached include for, example, 5- or 6-membered rings such as pyrrolidino and piperidino rings.

Suitably R^3 is a group



20 Examples of C_{1-4} alkyl groups (alone or as part of another group, e.g. C_{1-4} alkoxy) include methyl, ethyl, propyl or butyl which can be straight chain or branched.

Examples of halo groups include fluoro, bromo, chloro or iodo.

Particular compounds of structure (I) include :

- 25 4-chloro-3-[2-N,N-(dimethylamino)ethyl]-5-phenylindole,
 4-chloro-3-(2-aminoethyl)-5-phenylindole,
 4-chloro-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)-5-phenylindole,
 4-chloro-5-phenylindole-3-carboxaldehyde guanyldiazide,
 3-[2-(dimethylamino)ethyl]-5-phenylindole,
 30 3-(2-aminoethyl)-5-phenylindole,
 3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)-5-phenylindole,
 5-phenylindole-3-carboxaldehyde guanyldiazide,
 3-[2-(dimethylamino)ethyl]-5-(1-naphthyl)indole,
 3-(2-aminoethyl)-5-(1-naphthyl)indole,

- 3-[2-(dimethylamino)ethyl]-5-(2,6-dimethylphenyl)indole,
3-(2-aminoethyl)-5-(2,6-dimethylphenyl)indole,
4-chloro-3-[2-(dimethylamino)ethyl]-5-(6-methoxy-3-pyridyl)indole,
3-(2-aminoethyl)-4-chloro-5-(6-methoxy-3-pyridyl)indole,
5 4-chloro-5-(1,2-dihydro-6-oxo-3-pyridyl)-3-[2-(dimethylamino)ethyl]indole,
3-(2-aminoethyl)-4-chloro-5-(1,2-dihydro-6-oxo-3-pyridyl)indole,
5-(1,4-dihydro-4-oxo-1-pyridyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole,
3-(2-aminoethyl)-5-(2-pyridyl)indole,
3-[2-(dimethylamino)ethyl]-5-(2-pyridyl)indole,
10 3-[2-(dimethylamino)ethyl]-5-(4-fluorophenyl)indole,
3-(2-aminoethyl)-5-(4-fluorophenyl)indole,
3-(2-aminoethyl)-4-chloro-5-(4-fluorophenyl)indole,
4-chloro-3-[2-(N,N-dimethylamino)ethyl]-5-(4-fluorophenyl)indole,
3-[2-(N,N-dimethylamino)ethyl]-5-(4-methylphenyl)indole,
15 4-chloro-3-[2-(N,N-dimethylamino)ethyl]-5-(4-methylphenyl)indole,
3-(N-methylpiperidin-4-yl)-5-phenylindole,
5-(1,4-dihydro-4-oxo-1-pyridyl)-3-(N-methylpiperidin-4-yl)indole,
5-(2-cyanophenyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole,
5-(2-cyanophenyl)-3-(N-methylpiperidin-4-yl)indole,
20 3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)-5-(3-pyridyl)indole,
3-(N-methylpiperidin-4-yl)-5-(3-pyridyl)indole,
5-(4-methoxy-2-pyrimidinyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole,
5-(4-methoxy-2-pyrimidinyl)-3-(N-methylpiperidin-4-yl)indole,
5-(1,4-dihydro-4-oxo-2-pyrimidinyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole,
25 4-chloro-3-[2-(N,N-dimethylamino)ethyl]-5-(4-methoxyphenyl)indole,
3-[2-(N,N-dimethylamino)ethyl]-5-(4-methoxyphenyl)indole,
4-chloro-5-(4-chlorophenyl)-3-[2-(N,N-dimethylamino)ethyl]indole,
5-(4-chlorophenyl)-3-[2-(N,N-dimethylamino)ethyl]indole,
5-(4-chlorophenyl)-3-(2-aminoethyl)indole,
30 4-chloro-3-[2-(N,N-dimethylamino)ethyl]-5-(4-trifluoromethylphenyl)indole,
3-(2-aminoethyl)-5-(4-trifluoromethylphenyl)indole,
3-[2-(N,N-dimethylamino)ethyl]-5-(4-trifluoromethylphenyl)indole,
3-(2-aminoethyl)-5-(1,4-dihydro-4-oxo-1-pyridyl)indole,
5-(1,4-dihydro-4-oxo-1-pyridyl)-3-[2-(N,N-dimethylamino)ethyl]-indole,
35 5-phenyl-3-(1,2,5,6-tetrahydropyridin-4-yl)indole,
3-[2-(methylamino)ethyl]-5-phenylindole,
4-chloro-3-[2-(methylamino)ethyl]-5-phenylindole,
5-(6-methoxy-3-pyridyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole,

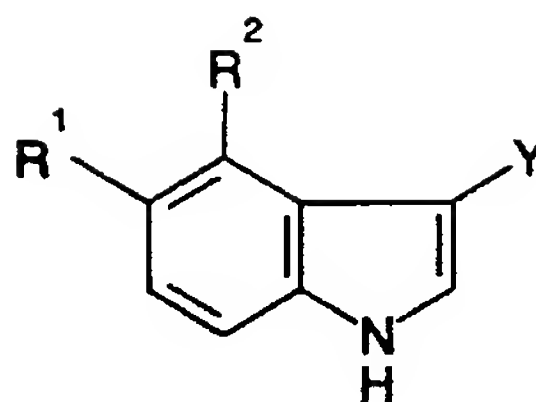
3-(4-hydroxy-N-methylpiperidin-4-yl)-5-(6-methoxy-3-pyridyl)indole,
 4-chloro-3-[2-(dimethylamino)ethyl]-5-(2-methoxy-3-pyridyl)indole,
 3-[2-(dimethylamino)ethyl]-4-methyl-5-phenylindole,
 3-[2-aminoethyl]-4-methyl-5-phenylindole,
 5 4-chloro-5-(1,2-dihydro-2-oxo-3-pyridyl)-3-[2-(dimethylamino)ethyl]indole,
 3-(2-aminoethyl)-4-chloro-5-(2-methoxy-3-pyridyl)indole,
 3-(2-aminoethyl)-4-chloro-5-(1,2-dihydro-2-oxo-3-pyridyl)indole,
 3-(2-aminoethyl)-4-chloro-5-(4-methoxyphenyl)indole,
 3-(2-aminoethyl)-5-(4-methoxyphenyl)indole,
 10 3-(2-aminoethyl)-4-chloro-5-(4-methylphenyl)indole,
 3-(2-aminoethyl)-5-(4-methylphenyl)indole,
 3-(2-aminoethyl)-4-chloro-5-(4-chlorophenyl)indole, and
 3-(2-aminoethyl)-4-chloro-5-(4-trifluoromethylphenyl)indole, and
 pharmaceutically acceptable salts, solvates or hydrates thereof.

15 Pharmaceutically acceptable acid addition salts of the compounds of structure (I) include, for example, those formed with inorganic acids e.g. hydrochloric, sulphuric, methanesulphonic or phosphoric acids and organic acids e.g. succinic, maleic, citric, (D) and (L) tartaric, acetic or fumaric acid. Other non-pharmaceutically acceptable salts e.g. oxalates may be used for example in the isolation of compounds of formula (I), and are
 20 included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of compounds of formula (I).

It will be appreciated that certain compounds of structure (I) for example where R^4 is other than hydrogen may contain an asymmetric centre. Such compounds will exist as two (or more) optical isomers (enantiomers). Both the pure enantiomers, racemic
 25 mixtures (50% of each enantiomer) and unequal mixtures of the two, are included within the scope of the present invention. Further, all diastereomeric forms possible (pure enantiomers and mixtures thereof) are within the scope of the invention.

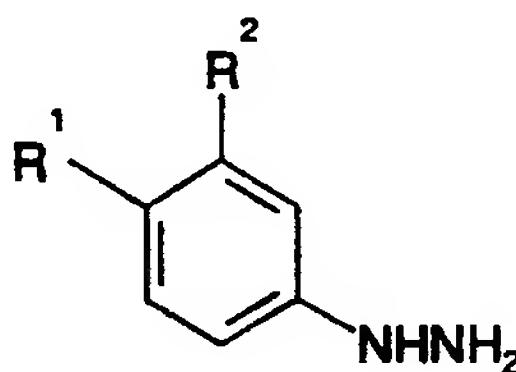
The compounds of the present invention can be prepared by processes analogous to those known in the art. The present invention therefore provides, in a further aspect, a
 30 process for the preparation of a compound of structure (I) or a salt, solvate or hydrate thereof, which comprises:

(a) for compounds in which R^3 is $C(R^4)(R^5)CH_2NR^6R^7$ reduction of a compound of structure (II):

**Structure (II)**

(in which R^1 and R^2 are as described for structure (I) and Y is a reducible group)
 optionally in the presence of a compound of the formula R^6R^7NH in which R^6 and R^7 are
 5 as described for structure (I); or

(b) reaction of a compound of structure (III) :

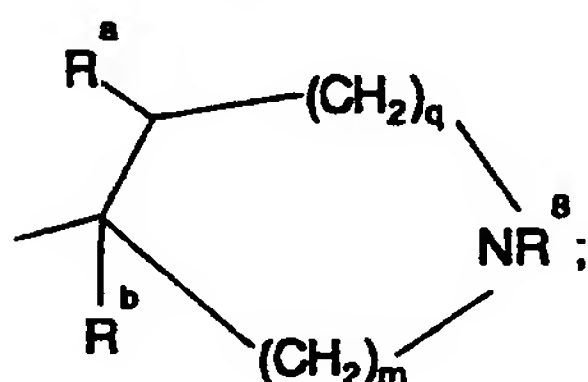
**Structure (III)**

(wherein R^1 and R^2 are as hereinbefore defined)
 10 or a salt thereof, with a compound of structure (IV) :

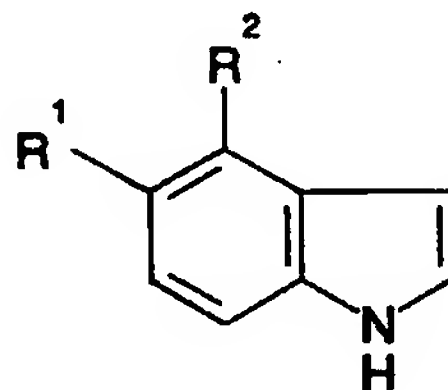
**Structure (IV)**

or a protected derivative (e.g. an acetal or ketal) thereof wherein R^3 is as described for
 15 structure (I); or

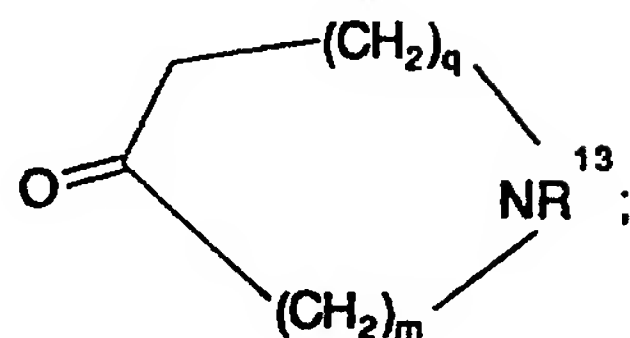
(c) for compounds where R^3 is



reaction of a compound of structure (V) :

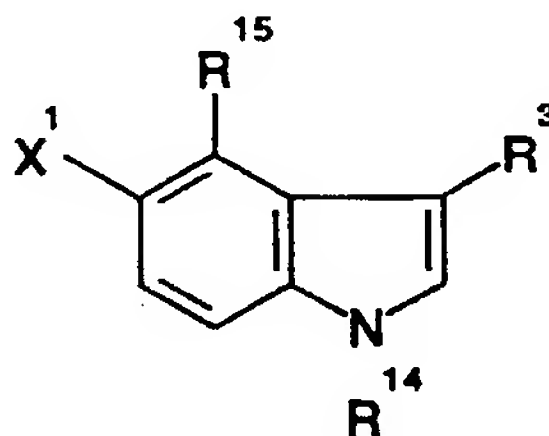
**Structure (V)**

(wherein R^1 and R^2 are as hereinbefore defined)
with a compound of structure (VI) :



Structure (VI)

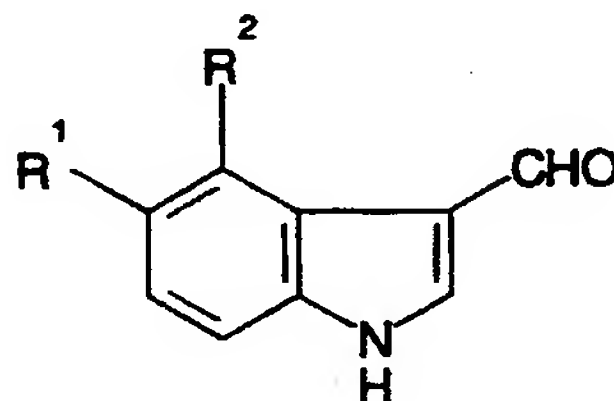
- 5 (wherein R^{13} is a N-protecting group or R^8 as hereinbefore defined and q and m are as hereinbefore defined), and if required removing the N-protecting group and/or dehydrating to form a compound wherein R^a and R^b together represent a bond and optionally thereafter hydrogenating to form a compound wherein R^a and R^b are both hydrogen;
- (d) reaction in the presence of a palladium catalyst of a compound of
- 10 structure (VII) :



Structure (VII)

- with a compound of formula R^1X^2 , wherein R^{14} is hydrogen or an N-protecting group, R^{15} is a group R^2 as hereinbefore defined or a precursor thereof, R^1 is as hereinbefore
- 15 defined and one of X^1 and X^2 is $B(OH)_2$ and the other is a suitable leaving group, and thereafter if required removing the N-protecting group and/or converting R^{15} to a group R^2 ;

(e) for compounds wherein R^3 is $-CH=NNHC(NH)NH_2$, reaction of a compound of structure (VIII) :



Structure (VIII)

wherein R^1 and R^2 are as hereinbefore defined with aminoguanidine or an acid addition salt thereof;

and thereafter optionally

- converting a group R^1 into another group R^1 ;
- converting a group R^2 into another group R^2 ;
- forming a pharmaceutically acceptable salt or hydrate thereof.

5 In compounds of structure (II) Y may be a group which is converted to $-C(R^4)(R^5)CH_2NR^6R^7$ when reduced in the presence of R^6R^7NH , in which case examples of Y include $-C(R^4)(R^5)CN$; and $-C(R^4)(R^5)CHO$. Alternatively Y may be a group which itself can be reduced to $-C(R^4)(R^5)CH_2NR^6R^7$, such groups including $-C(R^4)(R^5)CH_2NO_2$, $-C(R^4)(R^5)CH_2N_3$, $-COCONR^6R^7$, $-C(R^4)(R^5)CONR^6R^7$,
10 $-C(R^4)=CHNO_2$ and $-C(R^4)(R^5)CH_2NR^6COR^7$.

It will be appreciated that the precise method of reduction will depend on the nature of the group Y, such methods being well known in the art.

When Y represents $-C(R^4)(R^5)CHO$ or $-C(R^4)(R^5)CN$ the reaction between a compound of structure (II) and an amine R^6R^7NH is suitably carried out under reductive
15 amination conditions, for example, catalytic hydrogenation in the presence of the amine R^6R^7NH and a suitable solvent. Suitable catalysts include, for example, Raney nickel. Suitable solvents include, for example, C_{1-4} alkanols, in particular methanol. The reaction is carried out at ambient temperature or elevated temperature for as long as is necessary for the reaction to be complete. Preferred reaction conditions include, for
20 example for compounds in which R^6 and R^7 are both hydrogen, hydrogenation in methanolic ammonia in the presence of a Raney nickel catalyst; and where R^6 and R^7 are both C_{1-4} alkyl, for example methyl, hydrogenation in the presence of dimethylamine in methanol as solvent and Raney nickel as catalyst.

When Y represents a group $-C(R^4)(R^5)CH_2NO_2$, $-C(R^4)(R^5)CH_2N_3$,
25 $-COCONR^6R^7$, or $-C(R^4)(R^5)CONR^6R^7$ the reduction may be effected for example using allane (prepared from lithium aluminium hydride and sulphuric acid) or lithium aluminium hydride in a solvent such as tetrahydrofuran. Alternatively a group $-C(R^4)(R^5)CH_2NO_2$ may be reduced by catalytic hydrogenation, using for example palladium on charcoal or by treatment with cobalt boride prepared by treating a cobalt (II) salt such as cobalt chloride
30 with sodium borohydride in a suitable solvent such as methanol.

Reduction of a group $-C(R^4)(R^5)CH_2NR^6COR^7$ may be accomplished using a hydride such as lithium aluminium hydride.

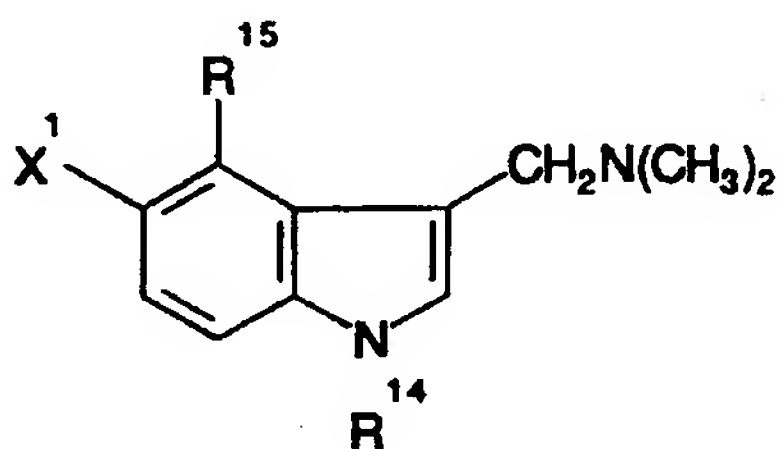
It will be appreciated that a variety of other substituents Y and methods of reduction are well-known in tryptamine chemistry, such as those described in
35 GB 2185020A, and may also be employed in process (a).

The intermediate compounds of structure (II) can be prepared by standard procedures.

Thus, compounds of structure (II) wherein Y represents $-CH_2CN$ may be prepared from the corresponding gramine (i.e. 3-dimethylaminomethyl) compound by

cyanation e.g. using potassium cyanide. The gramine derivative may be obtained by reaction of the 3-unsubstituted indole with bisdimethylaminomethane in the presence of acetyl chloride and in a suitable solvent, such as dichloromethane.

Alternatively the gramine derivative may be obtained by reaction of a compound
5 of structure (IX) :

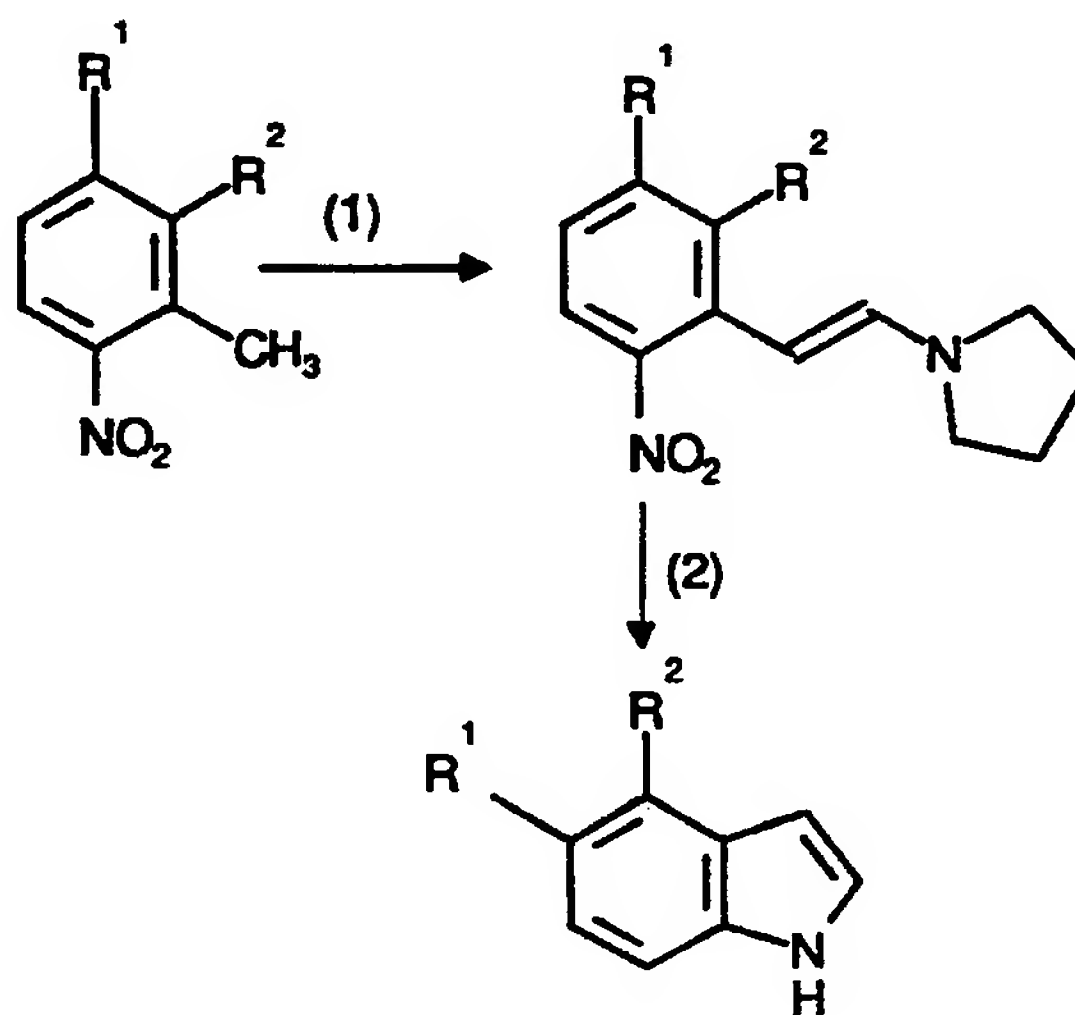


Structure (IX)

with a compound of formula R^1X^2 wherein R^1 , R^{14} , R^{15} , X^1 and X^2 are as hereinbefore defined in analogous manner to process (d).

10 A 3-unsubstituted indole may be prepared from an appropriately substituted nitrotoluene derivative according to the following reaction scheme 1 :

Scheme 1

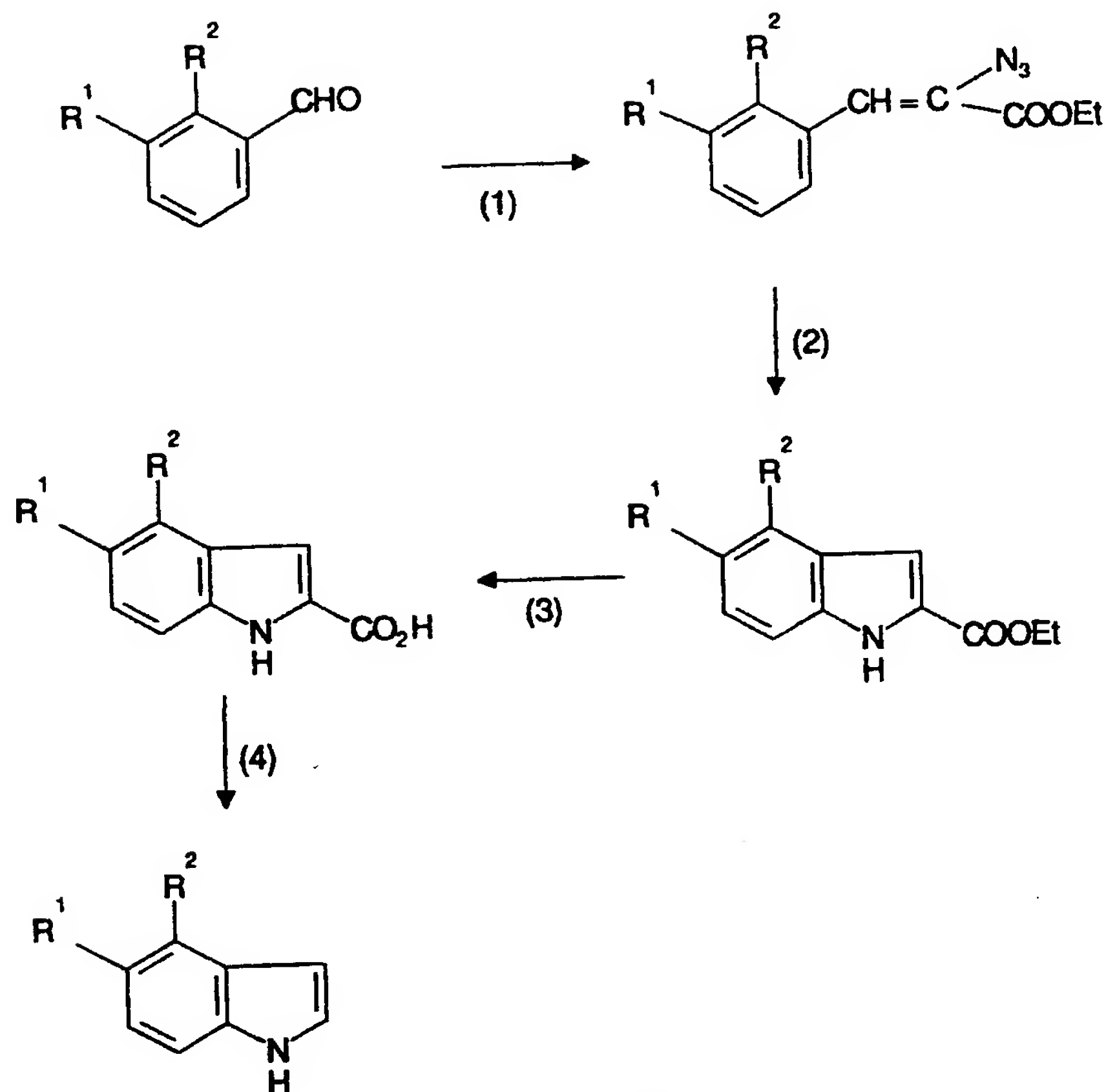


Structure (V)

15

- (1) $Me_2NCH(OEt)_2$, DMF, pyrrolidine
20 (2) $N_2H_4 \cdot H_2O$, Ni.

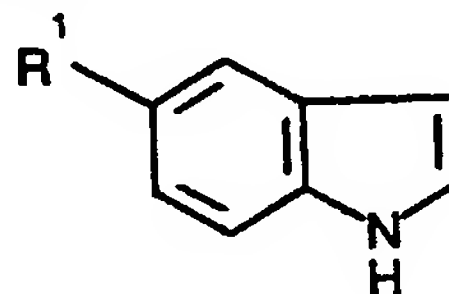
Alternatively a 3-unsubstituted indole may be obtained from an appropriately substituted benzaldehyde derivative according to the following reaction scheme 2 :



- (1) Ethyl azidoacetate/sodium ethoxide/ethanol
 (2) toluene, (reflux)
 (3) (i) Ethanol/sodium hydroxide (ii) HCl
 (4) heating.

When Y represents $-C(R^4)(R^5)CH_2NR^6COR^7$ a compound of structure (II) may be prepared by reacting a corresponding aminoethyl compound with an acylating agent, for example an anhydride such as acetic or propionic anhydride or a mixture of an acid with an anhydride e.g. formic acid and acetic anhydride. This intermediate provides a convenient method of preparing compounds of structure (I) wherein one of R^6 and R^7 is hydrogen and the other a C_{1-4} alkyl group.

A compound of structure (II) wherein Y represents $-COCONR^6R^7$ may be prepared from an indole of structure (X) :



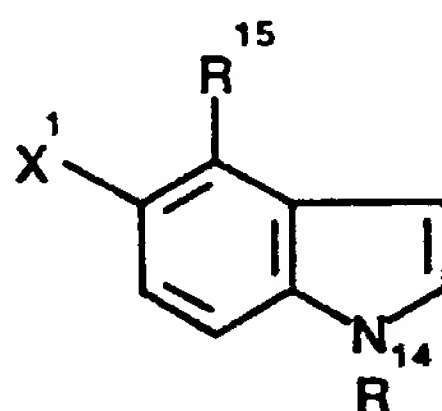
Structure (X)

by reaction with oxalyl chloride followed by an amine HNR^6R^7 and subsequently introducing the group R^2 . When R^2 is halogen e.g. iodine this may be introduced by reaction of a compound of structure II where R^2 is H and Y is $\text{COCONR}^6\text{R}^7$ with an appropriate halide e.g. potassium iodide in an acidic medium such as trifluoroacetic acid in the presence of thallium trifluoroacetate.

A compound of structure (II) wherein Y represents $-\text{C}(\text{R}^4)(\text{R}^5)\text{CHO}$ may be prepared for example by oxidation of the corresponding alcohol, using an oxidising agent such as pyridinium chlorochromate, or dimethylsulphoxide with oxalylchloride and triethylamine.

The alcohol may itself be obtained by a cyclisation analogous to process (b). The alcohol may also be converted to a halide derivative and thence to an azide using standard procedures, to give a compound of structure (II) wherein Y represents $-\text{C}(\text{R}^4)(\text{R}^5)\text{CH}_2\text{N}_3$.

A compound of structure (V) can be prepared by reacting a compound of structure (XI) :



Structure (XI)

with a compound of formula R^1X^2 , wherein R^1 , R^{14} , R^{15} , X^1 and X^2 are as hereinbefore defined in analogous manner to process (d) .

Cyclisation according to process (b) is a standard method for preparing indole compounds and may be effected by methods well known in the art, for example by heating a compound of structure (III) with a compound of structure (IV) in a non-aqueous solvent such as acetic acid or an aqueous or non-aqueous solvent e.g. an alcohol such as methanol in the presence of an acid catalyst such as hydrochloric acid or a Lewis acid such as boron trifluoride, or in the presence of an acidic ion exchange resin.

A compound of structure (III) may be obtained from the corresponding aniline derivative by diazotisation, for example using sodium nitrite and concentrated hydrochloric acid, and subsequent reduction.

In process (c) the reaction of a compound of structure (V) with a compound of structure (VI) is suitably performed in the presence of a base e.g. sodium methoxide in an organic solvent such as a C_{1-2} alkanol at ambient temperature or elevated temperature e.g. $30-50^\circ\text{C}$, conveniently at the reflux temperature of the reaction mixture. Under these reaction conditions the compound wherein R^a and R^b together represent a bond is formed by dehydration of the intermediate compound wherein R^a is hydrogen and R^b is hydroxy. Under suitable conditions both of these products can then be isolated in standard manner. Alternatively the reaction can be carried out under acidic conditions, e.g. in acetic acid at

elevated temperature (e.g. 30-100°C). These acidic conditions are particularly useful when R^2 is not hydrogen, e.g. when R^2 is Cl. When R^{13} is a N-protecting group for example *tert*-butoxycarbonyl this can be removed in standard manner for example by treatment with HCl in methanol or with trifluoroacetic acid. If desired the dehydrated product can be hydrogenated in standard manner to afford the compound wherein R^a and R^b are both hydrogen.

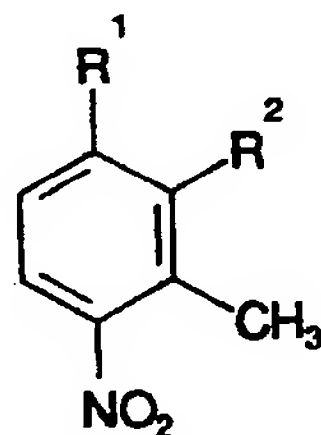
In process (d) suitable leaving groups for X^1 or X^2 include halo, such as bromo or iodo or trifluoromethanesulphonyloxy. The reaction is suitably performed in the presence of a palladium catalyst such as tetrakis (triphenylphosphine) palladium and a base such as triethylamine, barium hydroxide, sodium bicarbonate or sodium carbonate and, when X^1 or X^2 is trifluoromethanesulphonyloxy, a halide salt such as lithium chloride, in a solvent such as dimethylformamide, acetonitrile, toluene, benzene, tetrahydrofuran, ethanol, dimethoxyethane, water or mixtures thereof, at an elevated temperature (e.g. 30-150°C), preferably at the reflux temperature of the reaction mixture.

Suitable N-protecting groups include trialkylsilyl groups such as triisopropylsilyl which can be removed in standard manner, e.g. by treatment with tetra-*n*-butylammonium fluoride in a suitable solvent such as tetrahydrofuran or dichloromethane.

An example of a precursor of the group R^2 is hydrogen which is a suitable precursor for halogen as hereinbefore described for the introduction of such a group into a compound of structure (X).

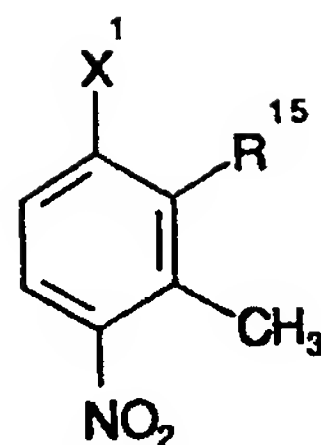
A compound of structure (VII), (IX) or (XI) wherein X^1 is $B(OH)_2$ is suitably prepared by reacting the organolithium or Grignard reagent, formed from the corresponding compound wherein X^1 is a leaving group such as halo e.g. bromo or iodo, with a tri- C_{1-4} alkylborate such as trimethyl, triisopropyl or tri-*n*-butyl borate in an organic solvent such as diethyl ether or tetrahydrofuran with cooling (e.g. -80 to 10°C), followed by aqueous work-up.

In a similar manner a compound of structure (XII) :



Structure (XII)

wherein R^1 and R^2 are as hereinbefore defined, which is the starting material of scheme 1, can be prepared by reacting a compound of structure (XIII) :



Structure (XIII)

with a compound of formula R^1X^2 , where R^1 , R^{15} , X^1 and X^2 are as hereinbefore defined.

5 In process (e) a compound of the structure (IX) is suitably reacted with an acid addition salt of aminoguanidine, e.g. the hydrochloride, in a suitable solvent such as a C_{1-4} alkanol, e.g. methanol or ethanol at ambient or preferably elevated temperature, e.g. 30-100°C, conveniently at the reflux temperature of the reaction mixture.

10 A compound of the structure (IX) can suitably be prepared by reacting a compound of structure (V) as hereinbefore defined with a Vilsmeier reagent formed from phosphoryl chloride and dimethylformamide followed by aqueous work-up in the presence of a base such as sodium hydroxide.

Suitable interconversions of R^1 groups, and of R^2 groups, will be apparent to those skilled in the art and can be carried out by standard procedures.

15 Acid addition salts of compounds (I) can be prepared by standard procedures, for example, by reaction with suitable organic and inorganic acids, the nature of which will be apparent to persons skilled in the art.

20 Compounds of structure (I) have affinity for the 5-HT₁-like receptor and are expected to be useful in treating disease states which require modulation of the 5-HT₁-like receptor. In particular the compounds are 5-HT₁-like agonists (or partial agonists) and as such are expected to have utility in medicine in the treatment and/or prophylaxis of migraine, and other conditions associated with cephalic pain, such as cluster headache, headache associated with vascular disorders and other neuralgia. They are also expected to have utility in the treatment or prophylaxis of portal hypertension.

25 In a further aspect, the invention provides a method of treatment of conditions which require alteration of the 5-HT₁-like receptor in particular migraine or portal hypertension which comprises administering to a subject in need thereof an effective amount of a compound of structure (I) or a pharmaceutically acceptable salt, solvate or hydrate thereof.

30 For use in medicine, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a compound of structure (I) or a pharmaceutically acceptable salt, solvate or hydrate thereof and a pharmaceutically acceptable carrier.

The compounds of the invention may be administered by any convenient route, for example by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

5 The compounds of structure (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water
10 with a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine
15 encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

20 Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

25 Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device.
30 Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochlorohydrocarbon. The
35 aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

40 Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

5 Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The pharmaceutically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose
10 of between 1 mg and 500 mg, preferably between 10 mg and 400 mg e.g. between 10 mg and 250 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg e.g. between 1 mg and 25 mg, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds
15 will be administered for a period of continuous therapy, for example for a week or more.

BIOLOGICAL DATA

5-HT₁-like Receptor Screen

RABBIT BASILAR ARTERY

20 Experiments were performed in intracranial arteries from rabbit isolated basilar artery in a similar method to one described previously (Parsons and Whalley, 1989. Eur J Pharmacol 174, 189-196.).

In brief, rabbits were killed by overdose with anaesthetic (sodium pentobarbitone). The whole brain was quickly removed and immersed in ice cold
25 modified Krebs's solution and the basilar artery removed with the aid of a dissecting microscope. The Krebs solution was of the following composition (mM) Na⁺ (120); K⁺ (5); Ca²⁺ (2.25); Mg²⁺ (0.5); Cl⁻ (98.5); SO₄²⁻ (1); EDTA (0.04), equilibrated with 95% O₂/5% CO₂. The endothelium was removed by a gentle rubbing of the lumen with a fine metal wire. Arteries were then cut into ring segments (ca 4-5 mm wide) and set up for
30 recording of isometric tension in 50 ml tissue baths in modified Krebs solution with the additional supplement of (mM); Na²⁺ (20); fumarate (10); pyruvate (5); L-glutamate (5) and glucose (10). The arteries were then placed under a resting force of 3-4 mN maintained at 37°C and the solution bubbled with 95% O₂/5% CO₂.

After tests for initial reactivity with 90 mM KCl depolarising solution and for
35 lack of acetylcholine-induced relaxation of 5-HT (10 mM) precontraction, cumulative concentration-effect curves (2 nM-60 mM) to 5-HT were constructed in the presence of ascorbate 200 mM, cocaine 6 mM, indomethacin 2.8 mM, ketanserin 1 mM and prazosin 1 mM.

Following a 45-60 min wash period, cumulative concentration-effect curves to the test compounds or 5-HT (as a time match control) were constructed in the presence of ascorbate, indomethacin, cocaine, ketanserin and prazosin.

The compounds of Examples 1, 2, 7, 11A, 11B, 12, 13, 14, 15B, 16, 18, 19, 22, 33, 34A, 38, 42, 43A, 43B, 44, 45A, and 45B had EC₅₀ values (concentration for half maximal contraction) in the range 0.03 to 1.5 μ M.

Example 1

4-Chloro-3-[2-N,N-(Dimethylamino)ethyl]-5-phenylindole

- 10 (a) Trifluoromethanesulphonic anhydride (10 g) was added to a cooled (ice bath) solution of 2-chloro-3-methyl-4-nitrophenol (6.65 g) and 4-N,N-dimethylaminopyridine (8.66 g) in dichloromethane (100 ml) over 30 minutes. After stirring for a further 4 hours the reaction mixture was poured into ice/2M hydrochloric acid (1:1, 100 ml) and stirred for 45 minutes. The organic phase was separated and solvent removed at reduced pressure.
- 15 The residue was dissolved in diethyl ether (200 ml), filtered and the filtrate evaporated at reduced pressure to give 2-chloro-6-nitro-3-trifluoromethanesulphonyloxytoluene (9.9 g).

¹H NMR δ (CDCl₃) 2.63(s,3H), 7.39(d,1H) and 7.82(d,1H).

- 20 (b) A mixture of 2-chloro-6-nitro-3-trifluoromethanesulphonyloxytoluene (9.7 g), phenylboric acid (3.7 g) tetrakis(triphenylphosphine)palladium (0) (1.26 g), lithium chloride (1.77 g), benzene (300 ml) ethanol (30 ml) and aqueous 2N sodium carbonate (37 ml) was boiled for 16 hours. After cooling to room temperature the reaction mixture was extracted with diethyl ether (2 x 200 ml) and the combined organic phases dried
- 25 (MgSO₄) and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, hexane \rightarrow 5% ethyl acetate/hexane eluant) to give 2-chloro-6-nitro-3-phenyltoluene (7.04 g).

¹H NMR δ (CDCl₃) 7.29(d,1H), 7.33-7.51(m,5H) and 7.76(d,1H).

30

- (c) A solution of 2-chloro-6-nitro-3-phenyltoluene (7.03 g) in dimethylformamide (60 ml) containing dimethylformamide diethyl acetal (4.95 g) and pyrrolidine (2.42 g) was heated at 120°C for 18 hours. Additional dimethylformamide diethyl acetal (2.09 g) and pyrrolidine (1.01 g) were added and heating continued for a further 3 hours. Solvent was
- 35 removed at reduced pressure and the residue dissolved in methanol (50 ml). Raney nickel (one spatula measure) was added followed by hydrazine hydrate (5.17 g) in three portions at 30 minute intervals. After stirring for a further 30 minutes after the addition of the final

portion of hydrazine hydrate the mixture was filtered solvent removed at reduced pressure and the residue column chromatographed (silica gel, ethyl acetate/hexane 0-20%) to give 4-chloro-5-phenylindole (2.49 g)

5 ^1H NMR δ (d_6 -dmso) 6.53(m,1H), 7.11(d,1H), 7.34-7.52(m,7H) and 11.50(br.s,1H).

(d) To an ice cooled solution of bis (dimethylamino)methane (1.31 g) in dichloromethane (50 ml), acetyl chloride (1.01 g) was added over 10 minutes, the mixture stirred for a further 10 minutes and 4-chloro-5-phenylindole (2.19 g) in dichloromethane
10 (30 ml) added. After stirring for 45 minutes the reaction mixture was basified with 10% sodium hydroxide and water (100 ml) added. The organic phase was separated washed with water (2 x 100 ml) dried (MgSO_4) and solvent removed at reduced pressure. The residue was dissolved in dimethylformamide (30 ml), potassium cyanide (2.38 g) and iodomethane (5.41 g) added. The mixture was stirred for 4 hours, diluted with water
15 (100 ml) and extracted with ethyl acetate (3 x 100 ml). The combined organic extracts were washed with water (4 x 100 ml), dried (MgSO_4) and solvent removed at reduced pressure to give 4-chloro-3-cyanomethyl-5-phenylindole (1.84 g).

20 ^1H NMR δ (d_6 -dmso) 4.21(s,2H), 7.11(d,1H), 7.35-7.61(m,7H) and 11.58(br.s,1H).

(e) A solution of 4-chloro-3-cyanomethyl-5-phenylindole (1.8 g) in methanol (50 ml) containing dimethylamine (25 ml) and Raney nickel (one spatula measure) was shaken under an atmosphere of hydrogen (40 psi) for 90 minutes. The mixture was filtered and the filtrate evaporated at reduced pressure. The residue was column chromatographed (silica
25 gel, 10% ammonia in methanol/dichloromethane 0 \rightarrow 5%) to give the free base of the title compound (0.446 g) which was converted to the oxalate salt by the addition of oxalic acid (0.28 g) and recrystallisation from methanol/diethyl ether m.p. 197-200°C.

Example 2

30 4-Chloro-3-(2-aminoethyl)-5-phenylindole

A solution of 4-chloro-3-cyanomethyl-5-phenylindole (0.83 g) in a mixture of methanol (50 ml) and saturated methanolic ammonia (50 ml) was shaken with Raney nickel (0.2 g) under hydrogen (40 psi) for 5 hours. Evaporation of the filtered solution gave the title compound as an oil, which was converted into its oxalate salt, 0.65 g, mp 197-198°C
35 (from methanol).

Example 3**4-Chloro-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)-5-phenylindole**

Orthophosphoric acid (2.5 ml, 2N) and 1-methyl-4-piperidone (0.3 ml) were added to a stirred solution of 4-chloro-5-phenylindole (546 mg) in acetic acid (10 ml) at 85°C. A
5 further five aliquots of 1-methyl-4-piperidone were added at 30 minute intervals and after 18 hours the temperature was raised to 100°C for a further 24 hours. The cool mixture was added to ice-ammonia (20 ml) and extracted with ethyl acetate and the extract was in turn extracted with 6N hydrochloric acid. The acid extract was neutralised with sodium bicarbonate and the resultant gum was extracted into ethyl acetate and the extract was
10 evaporated. Recrystallisation of the residue from 2-propanol gave 144 mg of the title compound as its hydrochloride salt mp 255-258°C.

Example 4**4-Chloro-5-phenylindole-3-carboxaldehyde guanylhyazone**

- 15 (a) 4-Chloro-5-phenylindole (569 mg) was added to Vilsmeier's reagent (from 0.25 ml phosphoryl chloride and 1.0 ml dimethylformamide) at a temperature $\leq 10^\circ\text{C}$. After 1 hour at 10°C the stirred mixture was heated at 35°C for 1 hour. The cool mixture was treated with ice (4 g) and a solution of sodium hydroxide (1.1 g) in water (3 ml) and then heated at the boiling point until evolution of dimethylamine had ceased. Filtration of the
20 chilled mixture gave 4-chloro-5-phenylindole-3-carboxaldehyde (627 mg, mp $80-82^\circ\text{C}$).
- (b) A solution of aminoguanidine hydrochloride (267 mg) in methanol (10 ml) was added to a solution of the above aldehyde (617 mg) in methanol (15 ml) and after 1 hour the stirred mixture was heated under reflux for 18 hours. The residue left after
25 evaporation was dissolved in water and treated with sodium bicarbonate (220 mg) to give a sticky solid. This was dissolved in methanol and treated with a solution of maleic acid (280 mg) in methanol. The solid left after evaporation was washed with petroleum ether and ether. Recrystallisation twice from ethyl acetate gave the maleate salt of the title compound as its three quarter hydrate (103 mg, mp $203-205^\circ\text{C}$).

30

Example 5**3-[2-(Dimethylamino)ethyl]-5-phenylindole**

- (a) A stirred mixture of 5-bromoindole (5.88 g), benzenboronic acid (5.49 g), tetrakis(triphenylphosphine)palladium (0.7 g), barium hydroxide (14.2 g),
35 dimethoxyethane (180 ml), and water (45 ml) was heated under reflux for 75 minutes. The volume of the mixture was reduced to about 50 ml by evaporation and the residue was

mixed with dichloromethane (200 ml) and water (200 ml) and filtered. The aqueous layer was extracted with dichloromethane (2 x 100 ml) and the combined organic extract was washed with water and brine. Evaporation of the dried solution gave an oil which was purified by flash chromatography (silica, petroleum ether/dichloromethane gradient) to give 4.43 g of 5-phenylindole, mp 63-64.5°C.

(b)(i) In a manner similar to that of Example 1(d), 5-phenylindole (1.55 g) gave 0.77 g of 3-cyanomethyl-5-phenylindole, mp 100-103°C.

(b)(ii) In an alternative procedure the intermediate 5-phenylgramine was prepared by heating a stirred mixture of 5-bromogramine (0.5 g), benzenboronic acid (0.27 g), sodium carbonate (0.42 g), tetrakis(triphenylphosphine)palladium (0.05 g), benzene (10 ml), ethanol (3 ml) and water (2 ml) under reflux for 2.5 hours. The filtered mixture was washed with water and then extracted with dilute hydrochloric acid. The extract was neutralised with sodium hydroxide solution and then solid potassium carbonate was added to give 5-phenylgramine (0.27 g, mp 130-131°C).

(c) In a manner similar to that of Example 1(e), hydrogenation of the above nitrile (0.76 g) gave a 1:1.4 mixture of the amino and dimethylamino products. The crude product in tetrahydrofuran (15 ml) was treated with di-t-butylidicarbonate (145 mg), the solvent was removed, and the residue was purified by flash chromatography (6 to 15% methanol in dichloromethane) to give, after elution of the 3-(2-t-butyloxycarbonylaminoethyl)-5-phenylindole, 0.14 g of 3-[2-(dimethylamino)ethyl]-5-phenylindole as an oil. This was converted into 0.12 g of the oxalate salt, mp 143.5-145°C (from 2-propanol).

Example 6

3-(2-Aminoethyl)-5-phenylindole

In a manner similar to that of Example 2, 3-cyanomethyl-5-phenylindole (0.77 g) gave 0.65 g of the title compound as its oxalate salt, mp 197-198°C (from methanol).

Example 7

3-(1-Methyl-1,2,3,6-tetrahydro-4-pyridyl)-5-phenylindole

(a) 1-Methyl-4-piperidone (506 mg) was added to a solution of 5-phenylindole (430 mg) in methanol (6 ml) containing 30% w/v sodium methoxide in methanol (2.55 ml) and

the solution was stirred under reflux for 3 hours. Filtration of the chilled mixture gave 464 mg of the title compound, mp 225-227°C (from methanol).

- (b) In an alternative procedure, a stirred mixture of 5-bromo-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole (1.0 g), benzenboronic acid (0.5 g), sodium carbonate (0.72 g), tetrakis(triphenylphosphine)palladium (0.2 g), benzene (30 ml), ethanol (9 ml) and water (4 ml) was heated under reflux for 1.5 hours. The filtered mixture was washed with water and then extracted with dilute hydrochloric acid. The extract was washed with ether and filtered to give the hydrochloride of the title compound (0.33 g, mp 272-274°C).

10

Example 8

5-Phenylindole-3-carboxaldehyde guanylhyazone

- (a) In a manner similar to that of Example 4(a), 5-phenylindole (1.0 g) gave 5-phenylindole-3-carboxaldehyde (1.1 g, mp 233-235°C).
- (b) In a manner similar to that of Example 4(b) the above aldehyde (443 mg) gave 235 mg of the title compound as its maleate salt mp 225.5-226.5°C (from ethanol/methanol).

15

Example 9

3-[2-(Dimethylamino)ethyl]-5-(1-naphthyl)indole (9A), and 3-(2-aminoethyl)-5-(1-naphthyl)indole (9B)

- (a) In a manner similar to that of Example 5(a), 1-naphthaleneboronic acid (3.71 g) gave 5-(1-naphthyl)indole as an oil (3.2 g).
- (b) In a manner similar to that of Example 1(d), 5-(1-naphthyl)indole (3.1 g) gave 3-cyanomethyl-5-(1-naphthyl)indole as a gum (2.1 g).
- (c) In a manner similar to that of Example 1(e), 3-cyanomethyl-5(1-naphthyl)indole (2.1 g) gave 288 mg of 3-[2-(dimethylamino)ethyl]-5-(1-naphthyl)indole, mp 146-148°C (from toluene). 3-(2-Aminoethyl)-5-(1-naphthyl)indole was obtained as a more polar component during the chromatographic purification of the above compound. The partially purified compound (322 mg) was treated with di-t-butylidicarbonate (180 mg) in tetrahydrofuran (5 ml) to give, after, flash chromatography with 30% ethyl acetate in hexane, 245 mg of the t-butyloxycarbonyl derivative. Hydrogen chloride was briefly

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passed into a solution of this derivative in dichloromethane, and the solution was chilled to give 3-(2-aminoethyl)-5-(1-naphthyl)indole hydrochloride (180 mg, mp 241-243°C).

Example 10

5 **3-[2-(Dimethylamino)ethyl]-5-(2,6-dimethylphenyl)indole (10A), and 3-(2-aminoethyl)-5-(2,6-dimethylphenyl)indole (10B)**

(a)(i) A stirred mixture of 1-triisopropylsilyl-5-indoleboronic acid (1.6 g), 2,6-dimethylbromobenzene (1.32 ml), barium hydroxide octahydrate (1.6 g), tetrakis(triphenylphosphine)palladium (0.29 g), dimethoxyethane (25 ml), and water (6 ml) was heated under reflux for 2.5 hours. The mixture was filtered, the aqueous solution was extracted with ether, and the combined organic extract was evaporated to an oil. Flash chromatography (silica, petroleum ether then mixtures with ether) gave 0.62 g of 5-(2,6-dimethylphenyl)-1-triisopropylsilylindole as a slowly crystallising oil, and then 0.31 g of 5-(2,6-dimethylphenyl)indole, mp 92-93°C (from cyclohexane). The crude protected indole (0.6 g) in tetrahydrofuran (10 ml) was treated briefly with 1.0 M tetrabutylammonium fluoride in tetrahydrofuran (1.6 ml). The residue after evaporation was dissolved in ether, the solution was washed with water and evaporated to an oil which gave further solid 5-(2,6-dimethylphenyl)indole (0.2 g) when triturated with petroleum ether. 1-Triisopropylsilyl-5-indoleboronic acid was prepared as follows. Triisopropylsilyl chloride (6.87 g) was added to the sodium salt prepared from 5-bromoindole (6.35 g) and sodium hydride (1.71 g, 50% suspension in oil) in dimethylformamide (32 ml) and the mixture was stirred at room temperature for 2 hours then poured into ice water (150 ml). The crude intermediate obtained by evaporation of the dichloromethane extract was purified by flash chromatography (silica, petroleum ether) to give 5-bromo-1-triisopropylindole (10.0 g) as an oil. The latter (3.52 g) in tetrahydrofuran (50 ml) was treated with t-butyl lithium in hexane (12.4 ml, 1.7 M) at -65°C during 15 minutes. The solution was kept at -65°C for 1 hour and then trimethylborate (11.4 ml) was added dropwise during 10 minutes at -65 to -55°C and the solution was kept a further 45 minutes at -65°C. Aqueous methanol (4 ml, 50%) was then added dropwise and the temperature was allowed to rise to ambient. After 2 hours the solution was added to water (150 ml) and the mixture was extracted with ether. Evaporation of the washed and dried extract gave 1-triisopropyl-5-indoleboronic acid as a glassy solid (3.2 g) which was used without purification.

35 (a)(ii) In an alternative procedure, a vigorously stirred mixture of 5-bromoindole (4.45 g), 2,6-dimethylbenzeneboronic acid (3.75 g), barium hydroxide octahydrate (7.89 g), tetrakis(triphenylphosphine)palladium (0.2 g), dimethoxyethane (110 ml) and water (27

ml) was heated under reflux for 8 hours. The cool mixture was filtered, the filtrate evaporated to low volume and the residue was distributed between ethyl acetate (100 ml) and water (75 ml). Hydrochloric acid was added to give a clear two phase system and the organic solution was separated, washed with water and brine, and evaporated to an oil.

- 5 Flash chromatography on silica with 8:1 petroleum spirit : ether gave 5-(2,6-dimethylphenyl)indole (0.94 g).

(b) In a manner similar to that of Example 1(d), 5-(2,6-dimethylphenyl)indole (0.9 g) gave 3-(cyanomethyl)-5-(2,6-dimethylphenyl)indole as an oil (0.3 g).

10

- (c) In a manner similar to that of Example 1(e), hydrogenation of the above nitrile gave a mixture of the two title compounds. Flash chromatography on silica gel with 200:10:1 dichloromethane:methanol:ammonia gave the less polar 3-[2-(dimethylamino)ethyl]-5-(2,6-dimethylphenyl)indole (80 mg) which was converted into its hemioxalate hydrate (60 mg, mp 237-239°C, from methanol), and the polar 3-(2-aminoethyl)-5-(2,6-dimethylphenyl)indole (50 mg) which was converted into its hemioxalate (30 mg, mp 252-254°C, from methanol-ether).

15

Example 11

- 20 **4-Chloro-3-[2-(dimethylamino)ethyl]-5-(6-methoxy-3-pyridyl)indole (11A) and 3-(2-aminoethyl)-4-chloro-5-(6-methoxy-3-pyridyl)indole (11B)**

- (a) In a similar manner to that of Example 1(b), 6-methoxy-3-pyridineboronic acid (7.0 g) and 2-chloro-6-nitro-3-trifluoromethanesulphonyloxytoluene (10.0 g) gave 2-chloro-3-(6-methoxy-3-pyridyl)-6-nitrotoluene (3.18 g). ¹H-nmr (CDCl₃) δ 2.63 (s, 3H);
25 7.39 (d, 1H); 7.83 (d, 1H).

(b) In a similar manner to that of Example 1(c), 2-chloro-3-(6-methoxy-3-pyridyl)-6-nitrotoluene (3.18 g) gave 4-chloro-5-(6-methoxy-3-pyridyl)indole (1.76 g, mp 118-121°C).

30

- (c) In a similar manner to that of Example 1(d), the above indole (1.6 g) gave 4-chloro-3-cyanomethyl-5-(6-methoxy-3-pyridyl)indole (0.76 g, mp 173-177°C).

- (d) In a similar manner to that of Example 1(e), the above nitrile gave a mixture of
35 the title compounds. Flash chromatography gave 4-chloro-3-[2-(dimethylamino)ethyl]-5-(6-methoxy-3-pyridyl)indole (428 mg, mp 140-144°C, after trituration with ether) and the primary amine which was purified further via its t-butyloxycarbonyl derivative (in a

similar manner to that in Example 9(a)) to give 3-(2-aminoethyl)-4-chloro-5-(6-methoxy-3-pyridyl)indole, isolated as its oxalate (130 mg, mp 213-216°C, from methanol).

Example 12

5 4-Chloro-5-(1,2-dihydro-6-oxo-3-pyridyl)-3-[2-(dimethylamino)ethyl]indole

Trimethylsilyl chloride (65 mg) was added to 4-chloro-3-[2-(dimethylamino)ethyl]-5-(6-methoxy-3-pyridyl)indole (100 mg) and sodium iodide (90 mg) in acetonitrile (2 ml) and the mixture was heated under reflux overnight. The cool mixture was poured into cold water and the residue left after evaporation was recrystallised from water to give the hydroiodide of the title compound (83 mg, mp 160-165°C).

Example 13

3-(2-Aminoethyl)-4-chloro-5-(1,2-dihydro-6-oxo-3-pyridyl)indole

In a manner similar to that of Example 12, 3-(2-aminoethyl)-4-chloro-5-(6-methoxy-3-pyridyl)indole (90 mg) gave the title compound, isolated as its oxalate salt (37 mg, mp 245-247°C, from methanol).

Example 14

5-(1,4-Dihydro-4-oxo-1-pyridyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole (a)

20 A stirred mixture of 5-aminoindole (2.48 g), 4H-pyran-4-one (2.01 g), hydrochloric acid (1.6 ml) and water (25 ml), was heated under reflux for 4 hours. The cooled mixture was neutralised with dilute sodium bicarbonate solution to deposit a gum which was washed with water and taken up in ethanol (60 ml). The residue left after evaporation was combined with the product obtained from a further 1.32 g of 5-aminoindole and purified by flash chromatography (silica, 10:1 dichloromethane:methanol) to give 5-(1,4-dihydro-4-oxo-1-pyridyl)indole (1.48 g, mp 240-241°C, from ethanol-ether).

(b) A mixture of the above indole (0.7 g), 1-methyl-4-piperidone (0.81 ml), methanolic sodium hydroxide (3.7 ml, 30% w/v) and methanol (10 ml), was heated under reflux for 8 hours and then evaporated to 50% of its original volume. The residue was diluted with water (20 ml), dilute hydrochloric acid added to pH 8, and the solution was concentrated to give the title compound as its hydrochloride salt (0.88 g, mp 250-252°C, from aqueous ethanol).

35

Example 15

3-(2-Aminoethyl)-5-(2-pyridyl)indole (15A), and 3-[2-(dimethylamino)ethyl]-5-(2-pyridyl)indole (15B)

(a) A stirred mixture of 1-triisopropyl-5-indoleboronic acid (4.48 g), 2-bromopyridine (4.42 g), sodium carbonate (2.76 g), benzene (80 ml), water (16 ml), ethanol (24 ml) and tetrakis(triphenylphosphine)palladium (0.81 g) was heated under reflux for 4.5 hours and then the organic solution was washed with water and with dilute hydrochloric acid. After evaporation of the organic solvent the crude 5-(2-pyridyl)-1-triisopropylindole was deprotected with 1.0 M tetrabutylammonium fluoride in tetrahydrofuran and the product subjected to flash chromatography (silica, 0 to 2% methanol in dichloromethane) to give crude 5-(2-pyridyl)indole (1.38 g, mp 125-128°C).

(b) In a manner similar to that of Example 1(d), the above indole (1.37 g) gave 3-(cyanomethyl)-5-(2-pyridyl)indole (0.26 g, mp 116-121°C, from dichloromethane/hexane).

(c) In a manner similar to that of Example 1(e), hydrogenation of the above nitrile (0.25 g) gave 3-(2-aminoethyl)-5-(2-pyridyl)indole, isolated as its oxalate (53 mg, mp 186-188°C, from methanol), and 3-[2-(dimethylamino)ethyl]-5-(2-pyridyl)indole isolated as its oxalate (100 mg, m.p. 104-108°C).

Example 16

3-[2-(Dimethylamino)ethyl]-5-(4-fluorophenyl)indole

(a) In a similar manner to that of Example 5(a) 5-bromoindole (3.53 g) and 4-fluorobenzeneboronic acid (3.78 g) gave 5-(4-fluorophenyl)indole (3.09 g, mp 95-96°C).

(b) In a similar manner to that of Example 1(d), the above indole (2.53 g) gave 3-(cyanomethyl)-5-(4-fluorophenyl)indole (1.93 g, mp 143.5-145°C, from ether/petroleum ether).

(c) In a similar manner to that of Example 1(e), the above nitrile (501 mg) gave an approximately equimolar mixture of the amino and dimethylamino products which was purified in a similar manner to that of Example 5(c) to give the title compound, isolated as its oxalate (170 mg, mp 195-196°C, from ethanol/methanol).

Example 17**3-(2-Aminoethyl)-5-(4-fluorophenyl)indole**

In a similar manner to that of Example 2, the nitrile from 16(b) above (400 mg) gave the title compound, isolated as its oxalate (120 mg, mp 202-203.5°C, from methanol).

5

Example 18**3-(2-Aminoethyl)-4-chloro-5-(4-fluorophenyl)indole**

(a) In a similar manner to that of Example 1(b), 4-fluorobenzeneboronic acid (7.8 g) gave 2-chloro-3-(4-fluorophenyl)-6-nitrotoluene (8.4 g, mp 61.5-62.5°C).

10 (b) In a variation on the method of Example 1(c), the enamine obtained from 5.7 g of the above nitrotoluene was dissolved in ethanol (15 ml) and the solution was added dropwise during 20 minutes to a stirred mixture of 30% aqueous titanium trichloride (65 ml) and ethanol (15 ml). After 3 hours the mixture was extracted with ether, the extract was washed with water and sodium carbonate solution, dried, and evaporated. The residue
15 was purified by column chromatography (silica gel, 3:2 petroleum ether:dichloromethane) to give 4-chloro-5-(4-fluorophenyl)indole (1.8 g, mp 93-94°C, from cyclohexane).

(c) In a similar manner to that of Example 1(d), the above indole (3.1 g) gave 4-chloro-3-cyanomethyl-5-(4-fluorophenyl)indole (2.0 g, mp 172-173°C, from cyclohexane-ether).

20 (d) In a similar manner to that of Example 2, the above nitrile (0.46 g) gave the oxalate of the title compound (0.37 g, mp 185.5-187°C, from methanol).

Example 19**4-Chloro-3-[2-(N,N-dimethylamino)ethyl]-5-(4-fluorophenyl)indole**

25 In a similar manner to that of Example 1(e), 4-chloro-3-cyanomethyl-5-(4-fluorophenyl)indole (0.51 g) gave the oxalate of the title compound (0.21 g, mp 215-216°C, from methanol).

Example 20**3-[2-(N,N-Dimethylamino)ethyl]-5-(4-methylphenyl)indole**

30 A stirred mixture of 5-bromo-3-[2-(N,N-dimethylamino)ethyl]indole (0.2 g), 4-methylbenzeneboronic acid (0.21 g), barium hydroxide (0.59 g), tetrakis(triphenylphosphine)palladium (16 mg), dimethoxyethane (6 ml) and water (1 ml) was heated under reflux in an inert atmosphere for 24 hours. The filtered mixture was
35 distributed between water and ethyl acetate and the organic extract was evaporated to an oil

(0.23 g). Column chromatography (silica, 100:10:1 dichloromethane:methanol:ammonia) gave the title compound which was isolated as its oxalate (0.04 g, mp 160-162°C, from methanol).

5 **Example 21**

4-Chloro-3-[2-(N,N-dimethylamino)ethyl]-5-(4-methylphenyl)indole

(a) In a similar manner to that Example 1(b), 4-methylbenzeneboronic acid (5.08 g) gave 2-chloro-3-(4-methylphenyl)-6-nitrotoluene (7.57 g, mp 92-94°C).

(b) In a similar manner to that of Example 1(c), the above nitrotoluene (5.95 g) gave
10 4-chloro-5-(4-methylphenyl)indole (0.45 g, mp °C, from).

(c) In a similar manner to that of Example 1(d), the above indole (0.9 g) gave 4-chloro-3-cyanomethyl-5-(4-methylphenyl)indole as an oil (1.91 g).

(d) In a similar manner to that of Example 1(e), the above nitrile (1.91 g) gave the oxalate of the title compound (0.15 g, mp 189-191°C, from methanol).

15

Example 22

3-(N-Methylpiperidin-4-yl)-5-phenylindole

3-(1-Methyl-1,2,3,6-tetrahydro-4-pyridyl)-5-phenylindole hydrochloride (0.33 g) in ethanol (40 ml) was shaken with 10% palladium on charcoal (0.1 g) under hydrogen at 45 psi until
20 hydrogenation was complete. Evaporation of the filtered solution gave a solid which was recrystallised from 2-propanol and then from ethanol to give the hydrochloride of the title compound (0.12 g, mp 247-249°C).

Example 23

25 **5-(1,4-Dihydro-4-oxo-1-pyridyl)-3-(N-methylpiperidin-4-yl)indole**

In a similar manner to that of Example 22, 5-(1,4-dihydro-4-oxo-1-pyridyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole hydrochloride (1.03 g) was hydrogenated to give the hydrochloride of the title compound (0.75 g, mp >300°C (decomposition), from ethanol).

30 **Example 24**

5-(2-Cyanophenyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole

(a) In a similar manner to that of Example 10(a)(i), 2-bromobenzonitrile (2.73 g) gave 5-(2-cyanophenyl)indole (0.75 g, mp 177-178°C, from cyclohexane).

(b) In a similar manner to that of Example 7(a), the above indole (0.74 g) gave the title
35 compound (0.76 g, mp 225.2-228°C, from methanol).

Example 25**5-(2-Cyanophenyl)-3-(N-methylpiperidin-4-yl)indole**

- 5 In a similar manner to that of Example 23, 5-(2-cyanophenyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole hydrochloride (0.35 g) gave the hydrochloride of the title compound (0.15 g, mp 292-294°C (decomposition), from methanol).

Example 26**3-(1-Methyl-1,2,3,6-tetrahydro-4-pyridyl)-5-(3-pyridyl)indole**

- 10 (a) In a similar manner to that of Example 10(a)(i), 3-bromopyridine (2.37 g) gave 5-(3-pyridyl)indole (0.64 g, mp 157-157.5°C, from acetonitrile).
(b) In a similar manner to that of Example 7(a), the above indole (0.63 g) gave the title compound (0.7 g, mp 231.5-234°C, from methanol).

15 **Example 27**

3-(N-Methylpiperidin-4-yl)-5-(3-pyridyl)indole

In a similar manner to that of Example 23, 3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)-5-(3-pyridyl)indole (0.47 g) gave the title compound as its dihydrochloride (0.26 g, mp 253-255°C, from ethanol).

20

Example 28**5-(4-Methoxy-2-pyrimidinyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole**

- (a) In a similar manner to that of Example 10(a)(i), 4-benzyloxy-2-chloropyrimidine (3.86 g) gave 5-(4-benzyloxy-2-pyrimidinyl)indole (0.7 g, mp 207-209°C, from acetonitrile).
25 (b) In a similar manner to that of Example 7(a), the above indole (0.69 g) gave the title compound (0.55 g, mp 188-189.5°C, from methanol).

Example 29**5-(4-Methoxy-2-pyrimidinyl)-3-(N-methylpiperidin-4-yl)indole**

- 30 In a similar manner to that of Example 22, 5-(4-methoxy-2-pyrimidinyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole (0.47 g) gave the title compound (0.3 g, mp 206-207.5°C, from 2-propanol).

Example 30**5-(1,4-Dihydro-4-oxo-2-pyrimidinyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole**

In a similar manner to that of Example 12, 5-(4-methoxy-2-pyrimidinyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole (0.54 g) gave the title compound isolated as its dihydrochloride salt (0.44 g, mp 238-242°C (decomposition), from ethanol).

Example 31**4-Chloro-3-[2-(N,N-dimethylamino)ethyl]-5-(4-methoxyphenyl)indole**

(a) In a similar manner to that of Example 1(b), 4-methoxybenzeneboronic acid (5.0 g) gave 2-chloro-3-(4-methoxyphenyl)-6-nitrotoluene (7.3 g, mp 87-89°C from dichloromethane/hexane).

(b) In a similar manner to that of Example 1(c), the above nitrotoluene (7.25 g) gave 4-chloro-5-(4-methoxyphenyl)indole (1.35 g, mp 105-106°C, after trituration with ether/hexane).

(c) In a similar manner to that of Example 1(d), the above indole (1.25 g) gave 4-chloro-3-cyanomethyl-5-(4-methoxyphenyl)indole (0.15 g, mp 131-134°C, from dichloromethane/hexane).

(d) In a similar manner to that of Example 1(e), the above nitrile (0.15 g) gave the title compound (0.04 g, mp 150-153°C, after trituration with methanol/ether).

Example 32**3-[2-(N,N-Dimethylamino)ethyl]-5-(4-methoxyphenyl)indole**

(a) In a similar manner to that of Example 5(a), 4-methoxybenzeneboronic acid (3.2 g) gave 5-(4-methoxyphenyl)indole (1.2 g, mp 118-120°C, from dichloromethane/hexane).

(b) In a similar manner to that of Example 1(d), the above indole (1.0 g) gave 3-cyanomethyl-5-(4-methoxyphenyl)indole (0.41 g, mp 141-143°C, from dichloromethane/hexane).

(c) In a similar manner to that of Example 1(e), the above nitrile (0.3 g) gave the oxalate of the title compound (0.06 g, mp 193-195°C, from methanol/ether).

Example 33**4-Chloro-5-(4-chlorophenyl)-3-[2-(N,N-dimethylamino)ethyl]indole**

(a) In a similar manner to that of Example 1(b), 4-chlorobenzeneboronic acid (8.0 g) gave 2-chloro-3-(4-chlorophenyl)-6-nitrotoluene (7.36 g, mp 87-89°C from dichloromethane/petroleum ether).

- (b) In a similar manner to that of Example 18(b), the above nitrotoluene (7.36 g) gave 4-chloro-5-(4-chlorophenyl)indole (2.34 g, mp 79-82°C, from cyclohexane).
- (c) In a similar manner to that of Example 1(d), the above indole (0.86 g) gave 4-chloro-5-(4-chlorophenyl)-3-cyanomethylindole (0.4 g, mp 193-195°C).
- 5 (d) In a similar manner to that of Example 1(e), the above nitrile (0.4 g) gave the oxalate of the title compound (0.13 g, mp 218-219°C, from methanol).

Example 34

10 5-(4-Chlorophenyl)-3-[2-(N,N-dimethylamino)ethyl]indole (34A) and 5-(4-chlorophenyl)-3-(2-aminoethyl)indole (34B)

- (a) In a similar manner to that of Example 5(a), 4-chlorobenzeneboronic acid (3.94 g) gave 5-(4-chlorophenyl)indole (1.86 g, mp 109-111°C, from toluene-hexane).
- (b) In a similar manner to that of Example 1(d), the above indole (1.82 g) gave 5-(4-chlorophenyl)-3-cyanomethylindole (0.85 g, mp 138-140°C).
- 15 (c) In a similar manner to that of Example 9(c), the above nitrile (0.85 g) gave the oxalate of 5-(4-chlorophenyl)-3-[2-(N,N-dimethylamino)ethyl]indole (0.18 g, mp 201-203°C, from methanol) and the hydrochloride of 5-(4-chlorophenyl)-3-(2-aminoethyl)indole (0.09 g, mp 290°C (decomposition)).

20 Example 35

4-Chloro-3-[2-(N,N-dimethylamino)ethyl]-5-(4-trifluoromethylphenyl)indole

- (a) In a similar manner to that of Example 1(b), 4-trifluorobenzeneboronic acid (11.11 g) gave 2-chloro-6-nitro-3-(4-trifluorophenyl)toluene (10.61 g, mp 53-63°C).
- (b) In a similar manner to that of Example 1(c), the above nitrotoluene (10.5 g) gave 25 4-chloro-5-(4-trifluorophenyl)indole (2.1 g, mp 123-127°C, from cyclohexane).
- (c) In a similar manner to that of Example 1(d), the above indole (2.0 g) gave 4-chloro-3-cyanomethyl-5-(4-trifluorophenyl)indole (0.5 g, mp 202-205°C, from toluene).
- (d) In a similar manner to that of Example 1(e), the above nitrile (0.5 g) gave the title compound (0.1 g, mp 187-189°C, from toluene).

30

Example 36

3-(2-Aminoethyl)-5-(4-trifluoromethylphenyl)indole

- (a) In a similar manner to that of Example 15(a), 4-bromotrifluoromethylbenzene (3.55 g) and 1-triisopropyl-5-indoleboronic (2.5 g) gave 5-(4-trifluoromethylphenyl)indole 35 (1.46 g, mp 148-148.5°C, from dichloromethane-petrol).

(b) In a similar manner to that of Example 1(d), the above indole (2.11 g) gave 3-cyanomethyl-5-(4-trifluoromethylphenyl)indole (1.26 g, mp 175-177°C, from dichloromethane-petrol).

(c) In a similar manner to that of Example 2, the above nitrile (1.1 g) gave the oxalate of the title compound (0.15 g, mp 214-215°C, from acetonitrile).

Example 37

3-[2-(N,N-Dimethylamino)ethyl]-5-(4-trifluoromethylphenyl)indole

In a similar manner to that of Example 20, 4-trifluoromethylbenzeneboronic acid (0.28 g) gave the title compound (75 mg, mp 155-156°C, from toluene).

Example 38

3-(2-Aminoethyl)-5-(1,4-dihydro-4-oxo-1-pyridyl)indole

(a) In a similar manner to that of Example 14(a), 5-aminogramine (4.0 g) and 4H-pyran-4-one (2.23 g) gave 5-(1,4-dihydro-4-oxo-1-pyridyl)gramine (3.28 g, mp 208-210°C (decomposition)).

(b) Methyl iodide (3.1 ml) was added to a stirred mixture of the above gramine (3.28 g) and potassium cyanide (3.09 g) in dimethylformamide (50 ml). After 2 hours at room temperature the mixture was evaporated and the residue was chromatographed (silica gel, 100:20:2→100:40:3 dichloromethane:methanol:ammonia) and the product was triturated with acetonitrile to give 3-cyanomethyl-5-(1,4-dihydro-4-oxo-1-pyridyl)indole (1.51 g, mp 206-208°C).

(c) In a similar manner to that of Example 2, the above nitrile (0.7 g) gave the oxalate of the title compound (0.52 g, mp 230-232°C (decomposition), from methanol).

Example 39

5-(1,4-Dihydro-4-oxo-1-pyridyl)-3-[2-(N,N-dimethylamino)ethyl]-indole

A mixture of 3-(2-aminoethyl)-5-(1,4-dihydro-4-oxo-1-pyridyl)indole (2.53 g), aqueous formaldehyde (37%, 1.2 ml), sodium cyanoborohydride (1.58 g), acetic acid (2.9 ml) and methanol (100 ml) was stirred at room temperature for 5 hours. The residue left after evaporation was digested with boiling methanol (150 ml) and the material contained in the digest was chromatographed (silica gel, 100:20:2→100:30:3 dichloromethane:methanol:ammonia) to give the title compound as a hydrated salt or complex with $\text{HCN} \cdot \text{BH}_3$ (1.67 g, mp 202-204°C, from ethanol).

Example 40**5-Phenyl-3-(1,2,5,6-tetrahydropyridiny-4-yl)indole**

A mixture of 5-phenylindole (0.3 g), 4-piperidone hydrochloride hydrate (0.6 g), 30% w/v sodium methoxide in methanol (2 ml) and methanol (6 ml) was heated under reflux for 8 hours. The cool mixture was diluted with water (to 25 ml) and then extracted with ethyl acetate (10 ml) and then with ether (30 ml). The organic extract was washed with water and then dilute hydrochloric acid (2 ml) was added to give the hydrochloride of the title compound (0.33 g, mp 265-267°C, from aqueous ethanol).

Example 41**3-[2-(Methylamino)ethyl]-5-phenylindole**

(a) A solution of 3-(2-aminoethyl)-5-phenylindole (from 0.86 g of the oxalate) in dichloromethane (25 ml) was stirred for 4 hours with triethylamine (0.4 ml) and 3-methyl-2-methylthiobenzothiazolium iodide (0.94 g). The mixture was washed with water and brine, dried, and evaporated to give crude 3-methyl-2-[2-(5-phenyl-3-indolyl)ethyl]imino-2,3-dihydrobenzothiazole (0.93 g).

(b) The above imino compound (0.92 g) was heated at 100°C under nitrogen with methyl 4-toluenesulphonate (0.67 g) for 1.5 hours. The cooled melt was triturated with ethyl acetate/ether to give crude 3-methyl-2-[N-(5-phenyl-3-indolyl)ethyl-N-methyl]benzothiazolium 4-toluenesulphonate (1.14 g).

(c) The above quaternary (1.14 g) was stirred for 3 hours with n-butylamine (0.2 ml) in dichloromethane (20 ml). The residue left after evaporation was taken up in ethanol (10 ml) and the solution was stirred with potassium hydroxide (0.56 g). After 2 hours water (15 ml) and brine (20 ml) were added and the mixture was extracted with ethyl acetate. Evaporation of the washed and dried extract gave a gum which was triturated with ether and then chromatographed (silica gel, 100:10:1 dichloromethane:methanol:ammonia) to give the title compound as a gum (0.18 g). The oxalate had mp 226-228°C, from methanol/ether.

Example 42**4-Chloro-3-[2-(methylamino)ethyl]-5-phenylindole**

(a) In a similar manner to that of Example 41(a), 3-(2-aminoethyl)-4-chloro-5-phenylindole oxalate (0.87 g) gave 3-methyl-2-[2-(4-chloro-5-phenyl-3-indolyl)ethyl]imino-2,3-dihydrobenzothiazole (0.71 g, mp 288-289°C, decomposition).

(b) In a similar manner to that of Example 41(b), but using a reaction temperature of 190°C, the above imino compound (0.7 g) gave crude 3-methyl-2-[N-(4-chloro-5-phenyl-3-indolyl)ethyl-N-methyl]benzothiazolium 4-toluenesulphonate (0.88 g).

(c) In a similar manner to that of Example 41(c), the above quaternary (0.86 g) gave
5 the title compound (0.17 g). The oxalate had mp 101-103°C, from methanol.

Example 43

**5-(6-Methoxy-3-pyridyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole (43A) and
3-(4-hydroxy-N-methylpiperidin-4-yl)-5-(6-methoxy-3-pyridyl)indole (43B)**

10 (a) In a similar manner to that of Example 5(a), 5-bromoindole (4.97 g) and 6-methoxy-3-pyridineboronic acid (5 g) gave 5-(6-methoxy-3-pyridyl)indole (1.89 g, mp 82-86°C).

(b) In a similar manner to that of Example 7(a), the above indole (1 g) gave 5-(6-methoxy-3-pyridyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole (0.27 g, mp 242°C,
15 decomposition, from methanol/ethyl acetate). Concentration of the crude product mother liquors gave 3-(4-hydroxy-N-methylpiperidin-4-yl)-5-(6-methoxy-3-pyridyl)indole (0.07 g, mp 205°C, decomposition, from methanol).

Example 44

20 **4-Chloro-3-[2-(dimethylamino)ethyl]-5-(2-methoxy-3-pyridyl)indole**

(a) In a similar manner to that of Example 1(b), 2-methoxy-3-pyridineboronic acid (7.2 g) and 2-chloro-6-nitro-4-trifluoromethanesulphonyloxytoluene (20.8 g) gave 2-chloro-5-(2-methoxy-3-pyridyl)-6-nitrotoluene (9.77 g, mp 87-90°C, from ether/hexane).

(b) In a similar manner to that of Example 1(c), the above nitrotoluene (8.36 g) gave
25 4-chloro-5-(2-methoxy-3-pyridyl)indole (3.9 g, mp 137-139°C, from dichloromethane/hexane).

(c) In a similar manner to that of Example 1(d), the above indole (3.0 g) gave 4-chloro-3-cyanomethyl-5-(2-methoxy-3-pyridyl)indole (1.33 g, mp 192-195°C, from ether/hexane).

30 (d) In a similar manner to that of Example 1(e), the above nitrile (0.4 g) gave the title compound (0.16 g, mp 198-200°C, after trituration with methanol/ether).

Example 45**3-[2-(Dimethylamino)ethyl]-4-methyl-5-phenylindole (45A) and 3-[2-Aminoethyl]-4-methyl-5-phenylindole (45B)**

- a) In a similar manner to that of Example 1(a), 3-hydroxy-2-methylbenzaldehyde (11.9 g) gave 2-methyl-3-trifluoromethanesulphonyloxybenzaldehyde (23 g).
- 5 (b) In a similar manner to that of Example 1(a), the above triflate (23 g) gave 2-methyl-3-phenylbenzaldehyde (11.6 g, mp 60-63°C, from petroleum ether).
- (c) A mixture of the above aldehyde (11.6 g) and ethyl azidoacetate (30.5 g) in ethanol (75 ml) was slowly added to ethanolic sodium ethoxide (from sodium, 5.4 g, and ethanol, 10 250 ml) maintained at between -15 and -5°C. The mixture was stirred at 0°C for 3 hours and was then allowed to warm up to room temperature overnight. The residue left after evaporation was distributed between ether and saturated aqueous ammonium chloride solution. The washed and dried ethereal extract was evaporated and the residue chromatographed (silica gel, 10% ether in petroleum ether) gave ethyl 3-(2-methyl-3-15 biphenyl)-2-azidopropeneoate (5.6 g, mp 66-68°C, from petroleum ether).
- (d) The above vinyl azide (7.5 g) in xylene (400 ml) was added dropwise over 1 hour to boiling xylene (1400 ml) in an inert atmosphere. After 3 hours the solution was evaporated to about 50 ml volume and allowed to stand to give ethyl 4-methyl-5-phenylindole-2-carboxylate (5.64 g, mp 161-164°C).
- 20 (e) The above ester (6.1 g) in a mixture of ethanol (50 ml) and dilute sodium hydroxide solution (25 ml) was heated under reflux for 1 hour. The warm mixture was then acidified with dilute hydrochloric acid to give a solid, which was dissolved in ether. Evaporation of the washed and dried solution gave 4-methyl-5-phenylindole-2-carboxylic acid (5.5 g, mp 250°C).
- 25 (f) The above acid (5.5 g) was taken in portions and heated (bath temperature 300°) until effervescence ceased (2-3 minutes). The melts were combined in ether and the solution evaporated to an oil which crystallised when allowed to stand. Recrystallisation from cyclohexane gave 4-methyl-5-phenylindole (3.45 g, mp 81-82°C).
- (g) In a similar manner to that of Example 1(d), the above indole (2.0 g) gave 3-cyanomethyl-4-methyl-5-phenylindole (1.5 g, mp 165-170°, from ethyl acetate).
- 30 (h) In a similar manner to that of Example 1(e), the above nitrile (1.2 g) gave 3-[2-(dimethylamino)ethyl]-4-methyl-5-phenylindole oxalate (0.42 g, mp 213-216°C, from methanol) and 3-[2-aminoethyl]-4-methyl-5-phenylindole (0.27 g, mp 216-220°C, from methanol).

Pharmaceutical formulations**Example A**

A tablet for oral administration is prepared by combining

5		Mg/Tablet
	Compound of formula (I)	100
	lactose	153
	starch	33
	crospovidone	12
10	microcrystalline cellulose	30
	magnesium stearate	2
		—
		330 mg

into a 9 mm tablet.

15

Example B

An injection for parenteral administration is prepared from the following

20

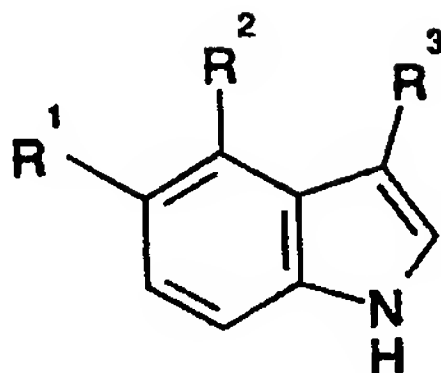
		% w:w
	Compound of formula (I)	0,50% (w:v)
	1M citric acid	30% (v:v)
	sodium hydroxide (qs)	to pH 3.2
25	water for injection BP	to 100 ml

The compound of formula (I) is dissolved in the citric acid and the pH slowly adjusted to pH 3.2 with the sodium hydroxide solution. The solution is then made up to 100 ml with water, sterilised by filtration and sealed into appropriately sized ampoules and vials.

30

CLAIMS:

1. A compound of structure (I):



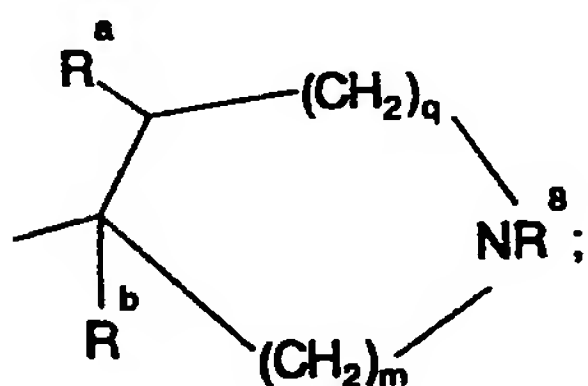
Structure (I)

in which

R^1 is an optionally substituted 6- to 10-membered aryl or heteroaryl ring;

R^2 is hydrogen, halogen, C_{1-4} alkyl, CN, NO_2 or CF_3 ;

R^3 is $C(R^4)(R^5)CH_2NR^6R^7$, $-CH=NNHC(NH)NH_2$ or



R^4 and R^5 are independently hydrogen or C_{1-4} alkyl;

R^6 and R^7 are the same or different and are each hydrogen or C_{1-4} alkyl or together with the nitrogen atom to which they are attached form a ring;

R^8 is hydrogen, C_{1-4} alkyl, or C_{3-6} alkenyl;

R^a is hydrogen and R^b is hydrogen or hydroxy, or R^a and R^b together represent a bond; and

q and m are independently 1 or 2;

and pharmaceutically acceptable salts, solvates and hydrates thereof.

2. A compound according to claim 1 where R^1 is optionally substituted phenyl or naphthyl.

3. A compound according to claim 1 where R^1 is an optionally substituted 6- to 10-membered heteroaryl ring containing from 1 to 4 nitrogen atoms.

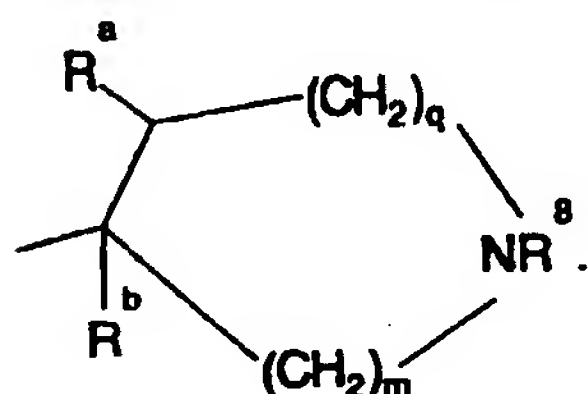
4. A compound according to any one of claims 1 to 3 wherein R^1 is unsubstituted or is substituted by 1 to 3 groups selected from halo, C_{1-4} alkyl, hydroxy, oxo, C_{1-4} alkoxy, $-CO_2R^9$, $-NHCOR^9$, $-CONR^{10}R^{11}$, $-SO_2NR^{10}R^{11}$, $-NHSO_2R^{12}$, NO_2 , $-NR^{10}R^{11}$, $NHCONH_2$, CN, CF_3 or CF_3O wherein R^9 to R^{11} are independently hydrogen or C_{1-4} alkyl and R^{12} is C_{1-4} alkyl.

5. A compound according to any one of claims 1 to 4 wherein R^2 is hydrogen or halogen.

5 6. A compound according to any one of claims 1 to 5 wherein R^3 is $-\text{CH}=\text{NNHC}(\text{NH})\text{NH}_2$ or $\text{C}(\text{R}^4)(\text{R}^5)\text{CH}_2\text{NR}^6\text{R}^7$ and R^4 and R^5 are both hydrogen or methyl.

7. A compound according to any one of claims 1 to 6 wherein R^6 and R^7 are
10 both hydrogen or methyl.

8. A compound according to any one of claims 1 to 5 where R^3 is a group



9. A compound of structure (I) selected from :
15 4-chloro-3-[2-N,N-(dimethylamino)ethyl]-5-phenylindole,
4-chloro-3-(2-aminoethyl)-5-phenylindole,
4-chloro-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)-5-phenylindole,
4-chloro-5-phenylindole-3-carboxaldehyde guanyldrazone,
3-[2-(dimethylamino)ethyl]-5-phenylindole,
20 3-(2-aminoethyl)-5-phenylindole,
3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)-5-phenylindole,
5-phenylindole-3-carboxaldehyde guanyldrazone,
3-[2-(dimethylamino)ethyl]-5-(1-naphthyl)indole,
3-(2-aminoethyl)-5-(1-naphthyl)indole,
25 3-[2-(dimethylamino)ethyl]-5-(2,6-dimethylphenyl)indole,
3-(2-aminoethyl)-5-(2,6-dimethylphenyl)indole,
4-chloro-3-[2-(dimethylamino)ethyl]-5-(6-methoxy-3-pyridyl)indole,
3-(2-aminoethyl)-4-chloro-5-(6-methoxy-3-pyridyl)indole,
4-chloro-5-(1,2-dihydro-6-oxo-3-pyridyl)-3-[2-(dimethylamino)ethyl]indole,
30 3-(2-aminoethyl)-4-chloro-5-(1,2-dihydro-6-oxo-3-pyridyl)indole,
5-(1,4-dihydro-4-oxo-1-pyridyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole,
3-(2-aminoethyl)-5-(2-pyridyl)indole,
3-[2-(dimethylamino)ethyl]-5-(2-pyridyl)indole,
3-[2-(dimethylamino)ethyl]-5-(4-fluorophenyl)indole,

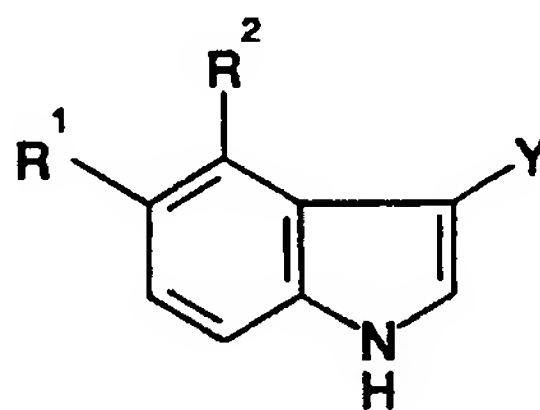
- 3-(2-aminoethyl)-5-(4-fluorophenyl)indole,
3-(2-aminoethyl)-4-chloro-5-(4-fluorophenyl)indole,
4-chloro-3-[2-(N,N-dimethylamino)ethyl]-5-(4-fluorophenyl)indole,
3-[2-(N,N-dimethylamino)ethyl]-5-(4-methylphenyl)indole,
5 4-chloro-3-[2-(N,N-dimethylamino)ethyl]-5-(4-methylphenyl)indole,
3-(N-methylpiperidin-4-yl)-5-phenylindole,
5-(1,4-dihydro-4-oxo-1-pyridyl)-3-(N-methylpiperidin-4-yl)indole,
5-(2-cyanophenyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole,
5-(2-cyanophenyl)-3-(N-methylpiperidin-4-yl)indole,
10 3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)-5-(3-pyridyl)indole,
3-(N-methylpiperidin-4-yl)-5-(3-pyridyl)indole,
5-(4-methoxy-2-pyrimidinyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole,
5-(4-methoxy-2-pyrimidinyl)-3-(N-methylpiperidin-4-yl)indole,
5-(1,4-dihydro-4-oxo-2-pyrimidinyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole,
15 4-chloro-3-[2-(N,N-dimethylamino)ethyl]-5-(4-methoxyphenyl)indole,
3-[2-(N,N-dimethylamino)ethyl]-5-(4-methoxyphenyl)indole,
4-chloro-5-(4-chlorophenyl)-3-[2-(N,N-dimethylamino)ethyl]indole,
5-(4-chlorophenyl)-3-[2-(N,N-dimethylamino)ethyl]indole,
5-(4-chlorophenyl)-3-(2-aminoethyl)indole,
20 4-chloro-3-[2-(N,N-dimethylamino)ethyl]-5-(4-trifluoromethylphenyl)indole,
3-(2-aminoethyl)-5-(4-trifluoromethylphenyl)indole,
3-[2-(N,N-dimethylamino)ethyl]-5-(4-trifluoromethylphenyl)indole,
3-(2-aminoethyl)-5-(1,4-dihydro-4-oxo-1-pyridyl)indole,
5-(1,4-dihydro-4-oxo-1-pyridyl)-3-[2-(N,N-dimethylamino)ethyl]-indole,
25 5-phenyl-3-(1,2,5,6-tetrahydropyridin-4-yl)indole,
3-[2-(methylamino)ethyl]-5-phenylindole,
4-chloro-3-[2-(methylamino)ethyl]-5-phenylindole,
5-(6-methoxy-3-pyridyl)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole,
3-(4-hydroxy-N-methylpiperidin-4-yl)-5-(6-methoxy-3-pyridyl)indole,
30 4-chloro-3-[2-(dimethylamino)ethyl]-5-(2-methoxy-3-pyridyl)indole,
3-[2-(dimethylamino)ethyl]-4-methyl-5-phenylindole,
3-[2-aminoethyl]-4-methyl-5-phenylindole,
4-chloro-5-(1,2-dihydro-2-oxo-3-pyridyl)-3-[2-(dimethylamino)ethyl]indole,
3-(2-aminoethyl)-4-chloro-5-(2-methoxy-3-pyridyl)indole,
35 3-(2-aminoethyl)-4-chloro-5-(1,2-dihydro-2-oxo-3-pyridyl)indole,
3-(2-aminoethyl)-4-chloro-5-(4-methoxyphenyl)indole,
3-(2-aminoethyl)-5-(4-methoxyphenyl)indole,
3-(2-aminoethyl)-4-chloro-5-(4-methylphenyl)indole,

3-(2-aminoethyl)-5-(4-methylphenyl)indole,
 3-(2-aminoethyl)-4-chloro-5-(4-chlorophenyl)indole, or
 3-(2-aminoethyl)-4-chloro-5-(4-trifluoromethylphenyl)indole, or
 a pharmaceutically acceptable salt, solvate or hydrate thereof.

5

10. A process for the preparation of a compound of structure (I) or a salt, solvate or hydrate thereof, which comprises :

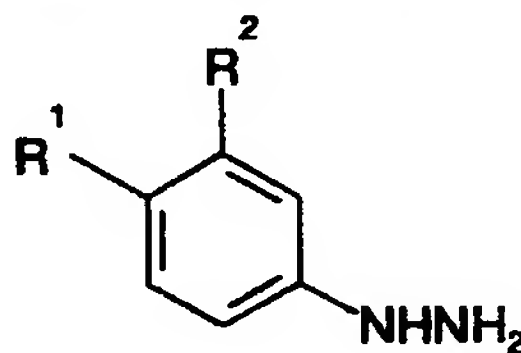
(a) for compounds in which R^3 is $C(R^4)(R^5)CH_2NR^6R^7$ reduction of a
 10 compound of structure (II):



Structure (II)

(in which R^1 and R^2 are as described for structure (I) and Y is a reducible group)
 optionally in the presence of a compound of the formula R^6R^7NH in which R^6 and R^7 are
 15 as described for structure (I); or

(b) reaction of a compound of structure (III) :



Structure (III)

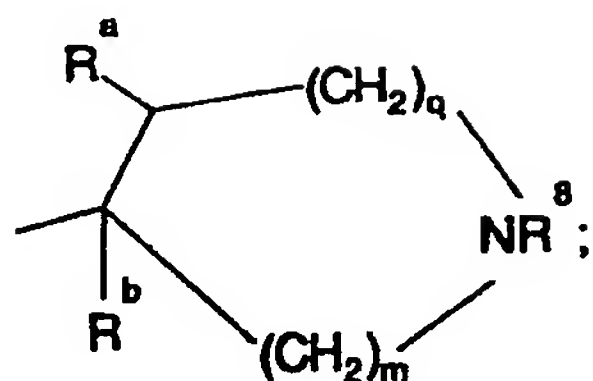
(wherein R^1 and R^2 are as hereinbefore defined)
 20 or a salt thereof, with a compound of structure (IV) :



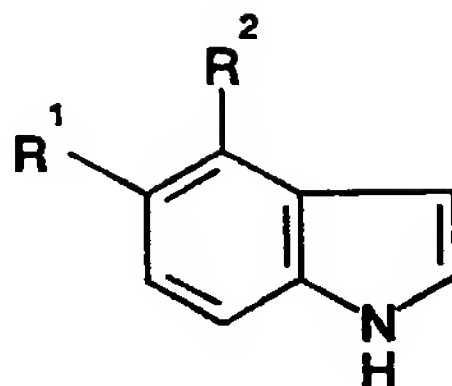
Structure (IV)

or a protected derivative (e.g. an acetal or ketal) thereof wherein R^3 is as described for
 structure (I); or

25 (c) for compounds where R^3 is

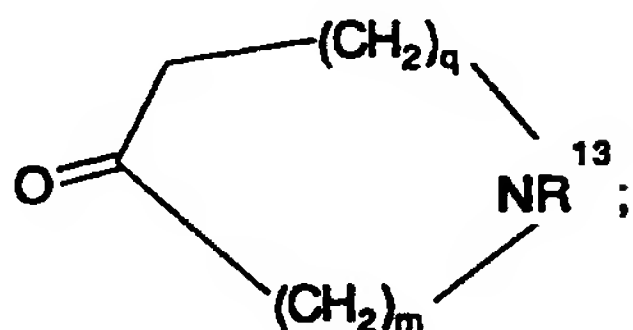


reaction of a compound of structure (V) :



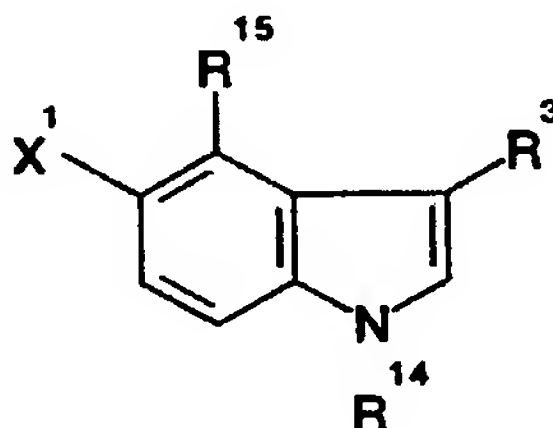
Structure (V)

- 5 (wherein R^1 and R^2 are as hereinbefore defined)
with a compound of structure (VI) :



Structure (VI)

- (wherein R^{13} is a N-protecting group or R^8 as hereinbefore defined and q and m are as
10 hereinbefore defined), and if required removing the N-protecting group and/or dehydrating
to form a compound wherein R^a and R^b together represent a bond and optionally
thereafter hydrogenating to form a compound wherein R^a and R^b are both hydrogen;
(d) reaction in the presence of a palladium catalyst of a compound of
structure (VII) :



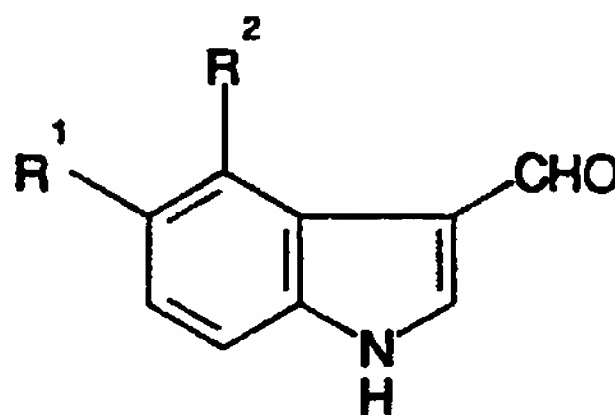
15

Structure (VII)

with a compound of formula R^1X^2 , wherein R^{14} is hydrogen or an N-protecting group,
 R^{15} is a group R^2 as hereinbefore defined or a precursor thereof, R^1 is as hereinbefore
defined and one of X^1 and X^2 is $B(OH_2)$ and the other is a suitable leaving group, and

thereafter if required removing the N-protecting group and/or converting R¹⁵ to a group R²;

(e) for compounds wherein R³ is -CH=NNHC(NH)NH₂, reaction of a compound of structure (VIII) :



Structure (VIII)

wherein R¹ and R² are as hereinbefore defined with aminoguanidine or an acid addition salt thereof;

and thereafter optionally

- converting a group R¹ into another group R¹;
- converting a group R² into another group R²;
- forming a pharmaceutically acceptable salt or hydrate thereof.

11. A compound of structure (I) as defined in claim 1 or a pharmaceutically acceptable salt, solvate or hydrate thereof for use as a medicament.

12. A pharmaceutical composition comprising a compound of structure (I) as defined in claim 1 or a pharmaceutically acceptable salt, solvate or hydrate thereof and a pharmaceutically acceptable carrier.

13. A method of treatment of a condition which requires modulation of the 5-HT₁-like receptor which comprises administering to a subject in need thereof an effective amount of a compound of structure (I) as defined in claim 1 or a pharmaceutically acceptable salt, solvate or hydrate thereof.

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/EP 93/03564

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D209/16 A61K31/40 C07D401/04 C07D209/14 C07D401/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 225 726 (GLAXO GROUP LTD.) 16 June 1987 * examples 16-21 *	1,12
A	EP,A,0 497 512 (MERCK SHARP & DOHME LTD.) 5 August 1992 see claims	1,12
A	WO,A,92 13856 (PFIZER INC.) 20 August 1992 see claims	1,12
A	EP,A,0 438 230 (MERCK SHARP & DOHME LTD.) 24 July 1991 see claims	1,12
A	EP,A,0 313 397 (THE WELLCOME FOUNDATION LTD) 26 April 1989 see claims	1,12
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

23 March 1994

Date of mailing of the international search report

20.04.94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 93/03564

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 13 is directed to a method of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No

PCT/EP 93/03564

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0225726	16-06-87	JP-A- 62167761 US-A- 4833153	24-07-87 23-05-89
EP-A-0497512	05-08-92	AU-B- 644939 AU-A- 1068092 CN-A- 1064485 JP-A- 5140151	23-12-93 06-08-92 16-09-92 08-06-93
WO-A-9213856	20-08-92	AU-A- 1263792 EP-A- 0571471 JP-T- 6500122	07-09-92 01-12-93 06-01-94
EP-A-0438230	24-07-91	AU-A- 6944091 CN-A- 1053429	25-07-91 31-07-91
EP-A-0313397	26-04-89	AU-A- 2418188 DE-A- 3881472 DE-T- 3881472 JP-A- 1146882 US-A- 5225431	27-04-89 08-07-93 16-12-93 08-06-89 06-07-93
EP-A-0505322	23-09-92	AU-A- 1309292 JP-A- 5086026	24-09-92 06-04-93